degrees of freedom (2–28 df/year) for temporal trends (Alhanti et al., 2016; Sarnat et al., 2015; Kim et al., 2012; Silverman and Ito, 2010). When examining all respiratory-related hospital admissions and ED visits, an examination of the control for temporal trends was limited to a few studies, all of which were conducted in Europe, (Stafoggia et al., 2013), in eight European cities, and (Lanzinger et al., 2016b), in the UFIREG project. Stafoggia et al. (2013) provided evidence that uniformly applying the same df/year across all cities could underestimate the $PM_{2.5}$ association. This was reflected by comparing results for models where 8 df/year was applied to each city or the df/year applied to each city was selected by minimizing the absolute value of the sum of the partial autocorrelation functions (PACF) to the base model, which employed a three-way interaction between year, month, and day of week to account for temporal trends. The authors reported that using 8 df/year attenuated the association while the PACF approach, which resulted in df/year ranging from 3–9 for each city, resulted in relatively unchanged $PM_{2.5}$ risk estimates. However, Lanzinger et al. (2016b) reported that $PM_{2.5}$ associations were relatively unchanged in models employing 3, 4, or 6 df/year to account for temporal trends.

In addition to conducting sensitivity analyses that examine control for temporal trends, some studies also assessed whether associations between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions and ED visits were sensitive to alternative weather covariates. Altering the lags (e.g., 0, 2-day average) for temperature and humidity in New Jersey (Gleason et al., 2014), or adjusting for maximum temperature in Atlanta, GA and St. Louis, MO (Alhanti et al., 2016) resulted in $PM_{2.5}$ associations that were relatively unchanged. Stafoggia et al. (2013) also examined the influence of including a longer temperature lag (i.e., 0–6 days) in the model to account for the potential prolonged effects of temperature on respiratory diseases. Replacing the 0–1-day lag temperature covariate with a 0–6-day lag term resulted in a relatively similar effect (lag 0–1: 1.36% [95% CI: 0.23, 2.49]; lag 0–6: 1.48% [95% CI: 0.29, 2.69]).

While most studies examined the influence of model specification on $PM_{2.5}$ associations with respiratory-related effects by focusing specifically on the inclusion of alternative weather covariates in statistical models, a few studies conducted analyses to examine whether there was evidence of model misspecification and potential residual confounding. In studies conducted in Atlanta, GA (Strickland et al., 2010) and St. Louis, MO (Sarnat et al., 2015), model misspecification was evaluated by examining associations with $PM_{2.5}$ concentrations on the day after an asthma ED visit (lag −1 day). In both studies the results of the base model are relatively similar to those reported for lag −1 day (i.e., (Strickland et al., 2010), warm season: RR = 1.05 [95% CI: 1.02, 1.08], lag 0–2, RR = 1.03 [95% CI: 1.00, 1.05], lag −1; (Sarnat et al., 2015), all-year: RR = 1.04 [95% CI: 1.01, 1.06], lag 0–2, RR = 1.02 [95% CI: 0.99, 1.04], lag −1). The smaller association, closer to the null in both studies, indicates that potential confounders of the relationship between short-term $PM_{2.5}$ exposure and asthma ED visits were adequately accounted for in the statistical model.

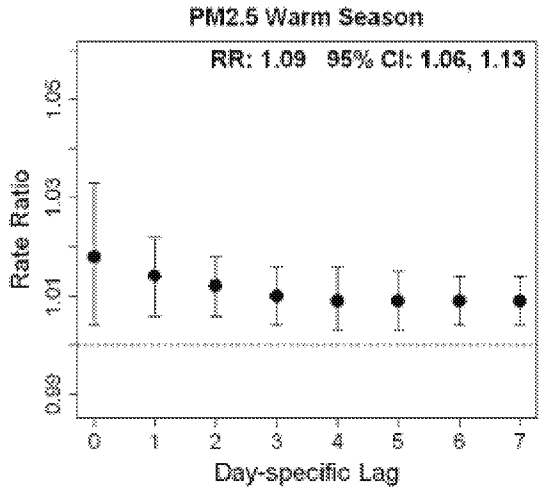
Across studies that examined alternative model specifications, replacing covariates used in the base model to account for the confounding effects of weather did not result in measurable changes in

$PM_{2.5}$ associations for respiratory-related effects. Additionally, there was little evidence that increasing the df/year to account for temporal trends influenced $PM_{2.5}$ associations; however, initial evidence indicates that applying the same df/year across individual cities in a multicity study may contribute to underestimating $PM_{2.5}$ risk estimates.

5.1.10.3 Lag Structure

An examination of associations between short-term $PM_{2.5}$ exposure and respiratory-related effects across different lag days can inform whether $PM_{2.5}$ elicits an immediate, delayed, or prolonged effect on health. As detailed throughout this chapter, evidence from studies that examine respiratory-related hospital admissions and ED visits indicates positive associations across single-day as well as multiday lags ranging from 0 to 4 days. However, to date many studies have not systematically evaluated different lags to examine the timing of effects, specifically whether there is evidence of an immediate (lag 0−1), delayed (lag 2−5), or prolonged (lag 0−5) $PM_{2.5}$ effect. An examination of lag structure in recent studies focusing on asthma, COPD, respiratory infections, and all respiratory-related hospital admissions and ED visits indicates that the strongest association in terms of magnitude and precision is generally within a few days after exposure for each of these outcomes, but there is some evidence demonstrating the potential for a prolonged $PM_{2.5}$ effect.

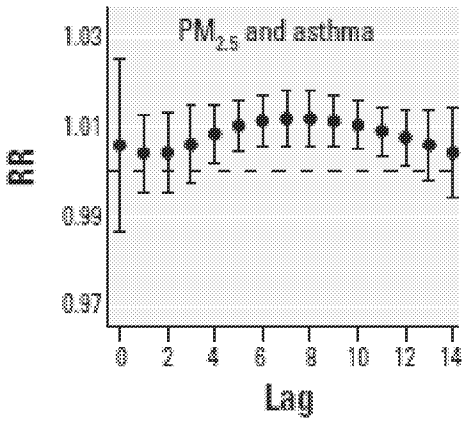
Among children in Atlanta, GA (Strickland et al., 2010) and individuals of all ages in Denver, CO (Kim et al., 2012), the pattern of associations for $PM_{2.5}$-asthma ED visits varied. In Strickland et al. (2010), lag 0 was reported to have the association largest in magnitude, but positive associations persisted across single-day lags of 1 to 7 days (Figure 5-14).



Source: Permission pending, Strickland et al. (2010).

Figure 5-14 Rate ratio and 95% confidence intervals for individual lag days from a constrained cubic polynomial distributed lag model examining associations between short-term $PM_{2.5}$ exposure and pediatric asthma emergency department (ED) visits in Atlanta, GA.

In contrast to the relatively immediate effect observed in Strickland et al. (2010), Kim et al. (2012) reported positive associations across the full range of lags examined (0−14), with the strongest associations, in terms of magnitude and precision, observed at lags 4 to 12 days, indicating a potential delayed response to short-term $PM_{2.5}$ exposure (Figure 5-15). When examining a distributed lag model of 0 to 7 days in Adelaide, Australia, Chen et al. (2016) observed an inconsistent pattern of associations with the strongest associations for asthma hospital admissions occurring at lags 2 and 4 days. When comparing results from multiday averages and distributed lag models, risk estimates were found to be larger in magnitude for the distributed lag model in Atlanta, GA (Strickland et al., 2010) (lag 0−2: RR = 1.05 [95% CI: 1.02, 1.08]; lag 0−7 DL: RR = 1.10 [95% CI: 1.07, 1.14]), but a similar magnitude of an association was observed at shorter and longer distributed lag models in St. Louis, MO (Sarnat et al., 2015) (lag 0−2: 1.04 [95% CI: 1.01, 1.06]; lag 0−4 DL: RR = 1.04 [95% CI: 1.01, 1.08]).



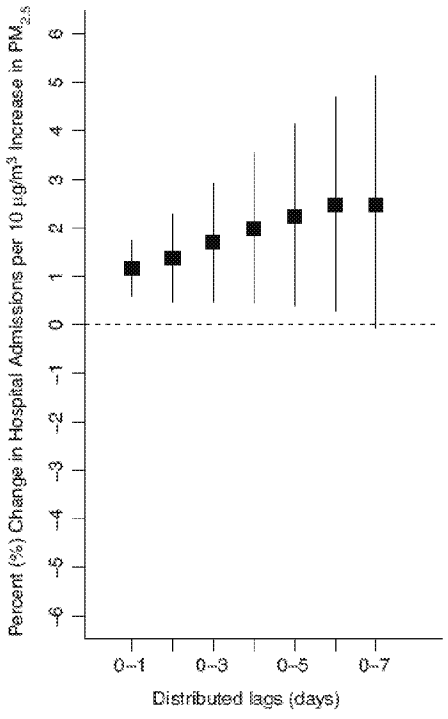
Source: Permission pending, Kim et al. (2012).

Figure 5-15 Relative risk and 95% confidence intervals for individual lag days from a constrained distributed lag model examining associations between short-term $PM_{2.5}$ exposure and asthma hospital admissions in Denver, CO.

Compared to asthma, the assessment of associations across different lags was limited for COPD and respiratory infection. Belleudi et al. (2010) examined both single-day and multiday lags (0 to 6 days, 0−1, 0−2, 0−5, and 0−6) for both COPD and lower respiratory tract infections. For COPD, the authors reported positive associations across a few single-day lags with the strongest association in terms of magnitude and precision observed at lag 0 (1.88% [95% CI: −0.27, 4.09]) and 2 (1.76 [95% CI: −0.18, 3.73]), with no evidence of an association for any of the multiday lags examined. However, for lower respiratory tract infections, positive associations were observed across single-day lags ranging from 1 to 5 days, but the magnitude of the association varied with the largest magnitude at lags 2 (2.82%) and 3 (3.04%). The multiple single-day lags reporting positive associations was further reflected when examining multiday averages, which provide evidence of a prolonged effect of short-term $PM_{2.5}$ exposure on lower respiratory tract infection (lag 0−5: (3.71 [95% CI: −0.57, 8.17]); lag 0−6: (3.62 [95% CI: −0.96, 8.42]).

Associations across different lags were further evaluated in recent studies focusing on all respiratory-related hospital admissions and ED visits. Overall, consistent, positive associations are reported across a range of single-day lags in multiple multicity studies (Bravo et al., 2017; Lanzinger et al., 2016b; Samoli et al., 2016a; Jones et al., 2015; Stafoggia et al., 2013). Some recent studies examined associations over a range of single-day lags through either a traditional single-day lag model or a distributed lag model. For example, Samoli et al. (2016a) and Jones et al. (2015) examined a series of single-day lags and reported positive association that were similar in magnitude across each individual lag, but confidence intervals were wide. In contrast to Samoli et al. (2016a) and Jones et al. (2015), Kim et al. (2012) did not report evidence of an association between short-term $PM_{2.5}$ exposure and

respiratory-related hospital admissions when examining the individual lag days of a 0 to 14 day constrained distributed lag model. However, the results for combinations of respiratory-related diseases differ from those observed for asthma hospital admissions in Kim et al. (2012) where, as previously mentioned, positive associations were observed at lags 4 to 12 days. In single-day lags of 0 to 2 days Bravo et al. (2017) reported a 0.79% increase (95% CI: 0.62, 0.97) at lag 0 in hospital admissions, but no evidence of an association at lags 1 or 2. However, when examining a distributed lag model of 0−7 days, the magnitude of the association increased as lag days increased, but confidence intervals did as well, providing some evidence of a potential prolonged $PM_{2.5}$ effect (Figure 5-16).



Source: Permission pending, Bravo et al. (2017).

Figure 5-16 Percent increase in respiratory-related hospital admissions for a distributed lag model up to 0−7 days for a 10 µg/m³ increase in 24-hour average $PM_{2.5}$ concentrations across 708 U.S. counties.

The results of Bravo et al. (2017) are consistent with both Lanzinger et al. (2016b) and Stafoggia et al. (2013) where positive associations were observed across each of the lags examined with the association with the largest magnitude observed for lag 0−5 in both studies. [(Lanzinger et al., 2016b): 2.8%, lag 0−1; 5.1%, lag 2−5; and 6.0%, lag 0−5; (Stafoggia et al., 2013): 0.49, lag 0−1; 1.1%, lag 2−5; and 1.4%, lag 0−5].

The assessment of associations across different lag structures for short-term $PM_{2.5}$ exposure and respiratory morbidity is further informed by analyses focusing on respiratory mortality. Multicity epidemiologic studies that examined cause-specific mortality in the 2009 PM ISA observed immediate effects with consistent positive associations for respiratory mortality at lags ranging from 0 to 2 days; however, these lags were selected a priori. Lippmann et al. (2013b), within the NPACT study, and Janssen et al. (2013), in a study conducted in the Netherlands, examined $PM_{2.5}$-respiratory mortality associations at single-day lags ranging from 0 to 3 days. While Lippmann et al. (2013b) reported the strongest association at lag 1, Janssen et al. (2013) reported evidence of associations larger in magnitude and with greater precision up to 3 days. Stafoggia et al. (2017), examining single-day lags ranging from 0 to 10 days, provide evidence that potentially supports the pattern of associations observed in both Lippmann et al. (2013b) and Janssen et al. (2013). The authors reported evidence of an immediate effect at lag 1, but also evidence of positive associations similar in magnitude at lags 3, 6, and 7 (quantitative results not presented). However, confidence intervals were wide, complicating the comparison of results across studies.

An examination of multiday lags by Lee et al. (2015) found a similar magnitude of an association across lags ranging from 0–1 to 0–4 days, which is consistent with the results of the studies examining single-day lags. However, Samoli et al. (2013), when examining lags indicative of immediate, delayed, and prolonged effects, reported evidence of an immediate $PM_{2.5}$ effect on respiratory mortality (0.72% [95% CI: −0.11, 1.6]; lag 0–1) that was larger in magnitude at longer lags (lag 2–5: 1.6% [95% CI: 0.62, 2.7]; lag 0–5: 1.9% [95% CI: 0.7, 3.1]). These results were further confirmed when examining single-day lags in a polynomial distributed lag model of 0–7 days, where associations were relatively consistent in magnitude from 0 to 2 days and then steadily increased out to 7 days.

Across the respiratory-related hospital admission and ED visit and mortality studies evaluated that conducted systematic evaluations of $PM_{2.5}$ associations across a range of lags, recent studies further support studies evaluated in the 2009 PM ISA that provided evidence of associations at lags ranging from 0–5 days. Studies of respiratory morbidity, specifically asthma and all respiratory-related hospital admissions and ED visits, along with more limited evidence from studies of COPD and respiratory infection, support that longer $PM_{2.5}$ exposures (i.e., 0–5-day lags) are associated with respiratory-related effects. Studies of respiratory mortality tended to support more immediate $PM_{2.5}$ effects (i.e., lags of 0 to 2 days), but initial evidence of stronger associations, in terms of magnitude and precision, at lags of 0–5 days is consistent with the pattern of associations observed in the hospital admission and ED visit studies.

5.1.10.4 The Role of Season and Temperature on $PM_{2.5}$ Associations

The examination of seasonal differences in $PM_{2.5}$ associations within studies that focus on respiratory-related hospital admissions and ED visits, as well as respiratory mortality, can provide

information that could be used to assess whether specific sources that vary by season are contributing to the $PM_{2.5}$ associations observed in all-year analyses. Additional studies that examine potential modification of $PM_{2.5}$ associations by temperature can further elucidate the impact of season on observed associations. Studies evaluated in the 2009 PM ISA, demonstrated seasonal variability in $PM_{2.5}$ associations with respiratory-related effects with some studies reporting associations in warmer months while others in colder months, which is further supported by recent studies. Fewer recent studies have examined potential modification of $PM_{2.5}$ associations by temperature.

5.1.10.4.1 Season

Recent studies have further examined the role of season on the relationship between short-term $PM_{2.5}$ exposure and respiratory-related effects, with the most extensive analyses focusing on asthma and all respiratory-related hospital admissions and ED visits. In studies of respiratory-related hospital admissions and ED visits, most often the warm season was defined as April–September, particularly for most northern U.S. cities, but in some cases the warm months encompassed May–October, such as for Atlanta, GA. $PM_{2.5}$-associated increases in asthma ED visits were observed in New Jersey in studies restricted to the warm season (Gleason and Fagliano, 2015; Gleason et al., 2014). Seasonal differences in associations are also supported by Malig et al. (2013) in a study of 35 California counties and asthma ED visits, which reported associations larger in magnitude in the warm compared to the cold season, as well as Stafoggia et al. (2013), in a study of eight European cities, which examined whether associations between short-term $PM_{2.5}$ exposure and all respiratory-related hospital admissions in the warm season were larger in magnitude than those observed in the all-year analysis. When restricting the analysis to the warm season (April–September), Stafoggia et al. (2013) reported a larger percent increase in respiratory-related hospital admissions (4.49% [95% CI: 1.72, 7.35]; lag 0–5) compared to the all-year analysis (1.36% [95% CI: 0.23, 2.49]; lag 0–5).

An examination of associations between short-term $PM_{2.5}$ exposure and asthma hospital admissions and ED visits in the cold season in U.S. locations were null except in New York, NY (Silverman and Ito, 2010; Ito et al., 2007). Additionally, (Rodopoulou et al., 2014) in a study examining all respiratory disease and acute respiratory infection ED visits in New Mexico, (Belleudi et al., 2010) in a study conducted in Rome, Italy focusing on respiratory infection ED visits, and (Lanzinger et al., 2016b) in a study of four European cities focusing on all respiratory-related hospital admissions reported evidence of associations larger in magnitude in the cold versus the warm season. The pattern of seasonal associations was also found to differ between two Australian cities, with an association larger in magnitude in the warm season in Sydney (Jalaludin et al., 2008) and in the cold season in Adelaide (Chen et al., 2016).

Additional studies conducted more refined analyses, focusing on all four seasons, to examine potential seasonal differences in $PM_{2.5}$ associations with respiratory-related hospital admissions and ED visits. For studies of asthma hospital admission and ED visit, an examination of $PM_{2.5}$ associations by the

four seasons is limited to Detroit, MI and Seoul, South Korea, but are consistent with each other in showing associations only in the spring (i.e., March–May) (Li et al., 2011 Kim, 2015, 3012210). However, studies focusing on all respiratory-related hospital admissions and ED visits reported a slightly different pattern of associations. Zanobetti et al. (2009), in a study of 26 U.S. counties reported the largest association in the spring (4.34% [95% CI: 2.19, 6.54]; lag 0–1) with the percent increase in respiratory-related hospital admissions ranging from 1.26–1.79% in the other seasons. Jones et al. (2015), in a study of New York state observed a slightly different pattern of associations across the seasons than Zanobetti et al. (2009). Focusing on lag 1, the authors reported associations largest in magnitude in the summer and fall with little evidence of an association in the winter and spring. Bell et al. (2015), in a study of 213 U.S. counties observed stronger associations with respiratory tract infection hospital admissions in spring (0.80% [95% CI: 0.02, 1.58]) and winter (0.40% [95% CI: −0.29, 1.10]), compared to the fall and spring where no evidence of an association was reported. The results from studies examining all four seasons support the results from studies that reported stronger associations during the warm season, but also provide some evidence that the greatest risk of $PM_{2.5}$-related respiratory effects may span into months traditionally defined as representing the cold season.

While studies in the 2009 PM ISA focusing on respiratory morbidity conducted seasonal analyses, studies focusing on mortality were limited to total (nonaccidental) mortality. These studies generally reported larger associations in warmer months (see Section 11.1.6.1) but resulted in uncertainty as to whether the same pattern of associations exists for cause-specific mortality, including respiratory mortality.

Recent multicity studies conducted in the U.S. (Dai et al., 2014; Lippmann et al., 2013a), Europe (Pascal et al., 2014; Samoli et al., 2013), and Asia (Lee et al., 2015) examined whether there was evidence of seasonal differences in the $PM_{2.5}$-respiratory mortality relationship. Within the NPACT study (Lippmann et al., 2013a), the examination of seasonal $PM_{2.5}$ associations resulted in a pattern of associations consistent with what was observed for total mortality (i.e., associations larger in magnitude during the warm season). However, compared to the all-year analysis, there was evidence of positive associations in the warm season across all lags examined with associations similar in magnitude (~0.5% increase) at lags 0, 1, and 3 days. There was also evidence of a positive association with respiratory mortality during the cold season, but only at lag 1 (0.40% [95% CI: −0.34, 1.1]). Dai et al. (2014), in a study of 75 U.S. cities reported results that were generally consistent with Lippmann et al. (2013a), but examined associations across all four seasons. Across seasons, the $PM_{2.5}$-respiratory mortality association was largest in magnitude during the spring (4.0% [95% CI: 2.9, 5.2]; lag 0–1), with positive, but smaller associations across the other seasons ranging from 0.58–1.1%.

Additional studies conducted in Europe report results consistent with those studies conducted in the U.S. In the MED-PARTICLES project, Samoli et al. (2013) examined short-term $PM_{2.5}$ exposure and respiratory mortality at lag 0–5 days and reported associations larger in magnitude in the warm season (6.5% [95% CI: 2.6, 10.5]) compared to the cold (1.7% [95% CI: 0.27, 3.2]). In France, Pascal et al.

(2014) reported similar results, but in an analysis of all four seasons. Associations between short-term $PM_{2.5}$ exposure and respiratory mortality were only positive during the spring and summer seasons, but confidence intervals were wide (quantitative results not presented).

Although the studies that examined U.S. and European cities provide consistent evidence of $PM_{2.5}$-respiratory mortality associations being larger in magnitude during warmer months (i.e., spring and summer), a study conducted in 11 east Asian cities observed a different pattern of associations. Lee et al. (2015) reported that $PM_{2.5}$ associations with respiratory mortality were larger in the cold season (1.3% [95% CI: 0.38, 2.2]) compared to the warm (0.63% [95% CI: −0.21, 1.5]). It is unclear why these results differ from the other studies, but mean $PM_{2.5}$ concentrations and mean temperature tended to be higher across the cities in Lee et al. (2015) compared to the cities in the other studies evaluated in this section.

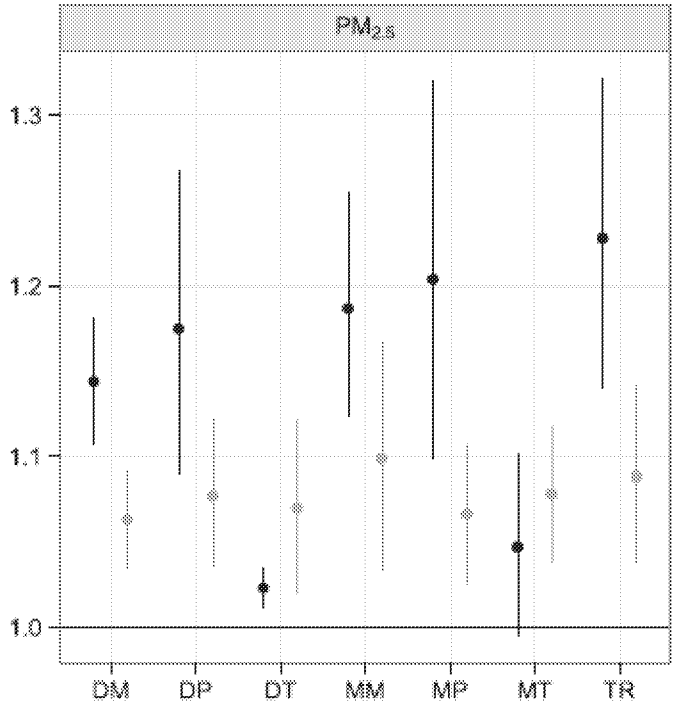
Across the multicity studies that examined seasonal associations, compared to studies of respiratory morbidity, results indicate that associations between short-term $PM_{2.5}$ exposure and respiratory mortality tend to be larger in magnitude during warmer parts of the year (i.e., spring and summer), specifically in locations where mean $PM_{2.5}$ concentrations and temperature are more like those observed in the U.S. These results are supported by studies that conducted more refined examinations of seasonal associations by each of the four seasons and observed associations larger in magnitude in the spring and summer.

In addition to traditional analyses that examine whether $PM_{2.5}$-respiratory-related hospital admission and ED visit associations vary by season; other studies have examined whether specific weather patterns influence associations. Hebbern and Cakmak (2015), in a study conducted in 10 Canadian cities, examined the association between short-term $PM_{2.5}$ exposure and asthma hospital admissions and whether the association was modified by specific synoptic weather patterns. Individual days were grouped into synoptic weather types based on temperature, humidity, and other factors. $PM_{2.5}$ associations with asthma hospital admissions were reported to be largest in magnitude for days classified as moist polar and transitional types and lowest in magnitude for dry tropical and moist tropical days, but interestingly these latter categories had higher $PM_{2.5}$ concentrations. However, when adjusting for aeroallergens, Hebbern and Cakmak (2015) observed that the difference in associations between weather types were absent.

Aeroallergens

While seasonal analyses can inform whether $PM_{2.5}$-asthma hospital admission and ED visit associations are influenced by weather, another factor tangentially related that has a strong seasonal component is aeroallergens. As detailed above, Hebbern and Cakmak (2015) reported that $PM_{2.5}$-asthma hospital admissions varied by synoptic weather pattern, but not when controlling for aeroallergens. However, in the models that controlled for aeroallergens, the RRs across all weather types, although attenuated, remained positive and were relatively similar, ranging from approximately 1.05−1.1 (Figure

5-17). Instead of controlling for the potential confounding effects of aeroallergens, Gleason et al. (2014), in a study conducted in New Jersey, examined whether the $PM_{2.5}$-asthma ED visit association varied across $PM_{2.5}$ quintiles depending on high and low levels of tree, grass, weed, and ragweed pollen. The authors observed no evidence of effect modification across the quintiles for high and low tree and grass pollen levels, and across all quintiles and levels of ragweed except for the combination of high ragweed and the highest quintile of $PM_{2.5}$ concentrations. However, when examining high ragweed pollen levels, as $PM_{2.5}$ concentrations increased there was evidence of effect modification (Table 5-17).



Note: Black circles represent before and grey circles represent after adjustment for aeroallergens.
DM = dry moderate; DP = dry polar; DT = dry tropical; MM = moist moderate; MP = moist polar; MT = moist tropical; TR = transitional weather types.
Source: Permission pending, Hebbern and Cakmak (2015).

Figure 5-17 Pooled relative risks across 10 Canadian cities by synoptic weather category.

Table 5-17 Odds ratios for quintile analyses in Gleason et al. (2014) from single-pollutant $PM_{2.5}$ analyses and analyses examining effect modification by high weed pollen days.

Study	$PM_{2.5}$ Analysis OR (95% CI)	Effect Modification Analysis OR (95% CI)
†Gleason et al. (2014) New Jersey, whole state 2004–2007	Lag 0: 0.53–6.1 μg/m^3: 1.0 (reference) 6.1–8.5 μg/m^3: 1.0 (0.95, 1.06) 8.5–11.4 μg/m^3: 0.99 (0.94, 1.04) 11.4–16.8 μg/m^3: 1.01 (0.96, 1.06) >16.9 μg/m^3: 1.05 (0.99, 1.11)	Effect modification of $PM_{2.5}$ associations by high weed pollen levels (lag 0–2) by $PM_{2.5}$ quintiles (lag 0): 0.53–6.1 μg/m^3: 1.0 (reference) 6.1–8.5 μg/m^3: 1.57 (1.14, 2.17) 8.5–11.4 μg/m^3: 1.53 (1.11, 2.12) 11.4–16.8 μg/m^3: 2.32 (1.61, 3.34) >16.9 μg/m^3: 2.51 (1.73, 3.64)

OR = odds ratio.
†Study published since the 2009 PM ISA.

5.1.10.4.2 Temperature

Instead of conducting traditional seasonal analyses, some recent studies examined whether there was evidence that higher temperatures modified the relationship between short-term $PM_{2.5}$ exposure and asthma hospital admissions and respiratory mortality. Cheng et al. (2015) examined whether specific temperatures modified the $PM_{2.5}$-asthma hospital admission association in Kaohsiung, Taiwan. The authors reported that $PM_{2.5}$ associations were larger in magnitude when analyses were restricted to days with lower temperatures, 13–25°C (RR = 1.10 [95% CI: 1.06, 1.13]) compared to days with higher temperatures (i.e., >25°C: RR = 1.02 [95% CI: 0.98, 1.06]).

Pascal et al. (2014) examined the impact of temperature on the $PM_{2.5}$-respiratory mortality relationship across nine French cities by comparing associations on warm and nonwarm days where warm days were defined as those days where the mean temperature exceed the 97.5th percentile of the mean temperature distribution. Pascal et al. (2014) reported no evidence of an interaction between $PM_{2.5}$ and warm days on respiratory mortality.

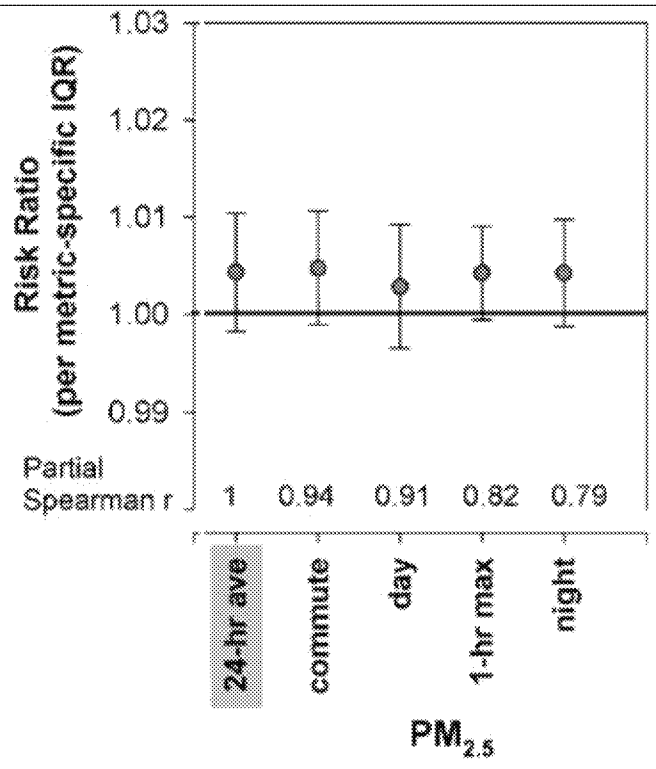
Additional studies conducted in Asia, although at higher mean $PM_{2.5}$ concentrations (i.e., in many cases >20 μg/m^3), also examined whether high temperatures modify the $PM_{2.5}$-respiratory mortality relationship. Li et al. (2015b) examined whether same-day temperature, either higher (>23.5°C) or lower temperatures (<2.6°C), modifies the $PM_{2.5}$-respiratory mortality relationship at lag 0 and 1. At lag 0, there was evidence of an association larger in magnitude at high temperatures (1.7% [95% CI: 0.92, 3.3]) compared to medium (0.76% [95% CI: −0.04, 2.0]), with no evidence of an association at low temperatures. However, at lag 1, the strongest evidence of an association was only for the medium

temperatures (0.80% [95% CI: −0.15, 1.8]). Sun et al. (2015) provides evidence contradictory to the results of Li et al. (2015b). At lag 0−1 days, the authors observed positive associations at high (≥25°C) and medium temperatures, ranging from 0.26−0.39%, but the magnitude of the association was much smaller than that observed for low temperatures (<22°C) (1.2% [95% CI: 0.51, 1.8]). Unlike Li et al. (2015b), Sun et al. (2015) did not specifically focus on the tails of the temperature distribution, which complicates the interpretation of the results between the two studies, especially considering the low temperature category in Sun et al. (2015) is relatively similar to the high temperature category in Li et al. (2015b). Overall, the evidence across studies is inconclusive as to whether specific temperature ranges modify the association between short-term $PM_{2.5}$ exposure and respiratory mortality.

5.1.10.5 Averaging Time of $PM_{2.5}$ Concentrations

Collectively, the combination of studies evaluated in the 2009 PM ISA and within this section largely support an association between short-term $PM_{2.5}$ exposures and increases in respiratory-related hospital admissions and ED visits, specifically when using a 24-hour average $PM_{2.5}$ concentration averaging time. To date, very few studies have examined associations with subdaily averaging times for $PM_{2.5}$ concentrations (e.g., 1-hour max), with some evidence indicating associations between ED visits and 1-hour max $PM_{2.5}$ concentrations. Previously, in Bronx, NY, RRs for asthma ED visits were similar in magnitude for 24-hour average and 1-hour max $PM_{2.5}$ concentrations (ATSDR, 2006). The two averaging times were found to be highly correlated ($r = 0.78$), but the spatiotemporal variability of 1-hour max concentrations was not reported. Similarly, other studies that examined subdaily averaging times have not provided information on the spatiotemporal variability of other exposure metrics, such as 3-hour average or 6-hour average $PM_{2.5}$ concentrations, which were examined in studies conducted in six Canadian cities (Stieb et al., 2009) and Seoul, South Korea (Kim et al., 2015)]. However, in both studies, the authors reported no evidence of an association between 24-hour average $PM_{2.5}$ concentrations and asthma ED visits, nor was there evidence of an association using the subdaily averaging times.

Darrow et al. (2011) systematically examined a series of averaging times to assess whether the 24-hour exposure metric was appropriate. The authors examined several subdaily averaging times (i.e., 1-hour max, commute time average [7−10 a.m. and 6−9 p.m.], daytime average [8 a.m.−7 p.m.], and nighttime average [12−6 a.m.]) in addition to the traditional 24-hour average when examining the relationship between short-term $PM_{2.5}$ exposure and respiratory-related ED visits. The averaging times were found to be highly correlated with one another with $r = 0.79$−0.94, which is consistent with ATSDR (2006). Across the averaging times examined, the authors reported relatively consistent positive associations of similar magnitude, but confidence intervals were wide (Figure 5-18).



Source: Permission pending, Darrow et al. (2011).

Figure 5-18 Association between short-term $PM_{2.5}$ exposure and respiratory-related emergency department (ED) visits in Atlanta, GA at lag 1 for 24-hour average and subdaily exposure metrics.

While hospital admission and ED visit studies can examine alternative averaging times for the exposure metric if ambient monitoring data is available, panel studies using personal monitors can examine more refined time scales of exposure but are limited to studies of pulmonary inflammation and lung function. A strength of studies of pulmonary inflammation is examination of the hourly lag structure of $PM_{2.5}$ associations. Most (Barraza-Villarreal et al., 2008; Rabinovitch et al., 2006; Mar et al., 2005) but not all (Berhane et al., 2011) results show an increase in inflammation with increases in $PM_{2.5}$ concentration averaged over the preceding 1 to 11 hours. Additional support is provided by associations with mean personal $PM_{1.5}$ exposure in nonhome/school locations (Rabinovitch et al., 2016). Associations also were observed with 1-hour or 8-hour maximum $PM_{2.5}$ that were larger than those for 24-hour average $PM_{2.5}$ (Delfino et al., 2006; Rabinovitch et al., 2006). Maximum concentrations occurred before inflammation was measured. Some results indicate that $PM_{2.5}$ exposure may have a rapid and transient effect on pulmonary inflammation in people with asthma. For Seattle, WA and Riverside and Whittier, CA, distributed lag models show an increase in eNO with the 1-hour average $PM_{2.5}$ concentration up to 5 or 10 hours prior but not with longer lags of 24–48 hours (Delfino et al., 2006; Mar et al., 2005). eNO measured at well-defined intervals after a scripted 2-hour exposure during morning commutes increased

3 hours post-exposure (Mirabelli et al., 2015). Longer lags were not examined, and a similar previous study did not observe any changes up to 22 hours after exposure (McCreanor et al., 2007). It is important to note that most recent studies examined 24-hour or multiday average $PM_{2.5}$, which may explain the inconsistency in associations observed (see section on eNO). However, studies evaluated in the 2009 PM ISA also used 24-hour or multiday average $PM_{2.5}$ concentrations and reported positive associations (Liu et al., 2009; Allen et al., 2008; Delfino et al., 2006).

Additional studies examined subdaily averaging times through 1 to 8-hour scripted outdoor exposures near pollution sources. Epidemiologic studies of scripted outdoor exposures examined $PM_{2.5}$ at high-traffic locations and found inconsistent results with respect to respiratory effects in healthy populations. Among epidemiologic studies of adults commuting by car, bus, or bicycle, working as school crossing guards or traffic police, or spending time in high-traffic areas, $PM_{2.5}$ was associated with increases in pulmonary inflammation (Mirowsky et al., 2015; Zhao et al., 2015; Steenhof et al., 2013) or decreases in lung function (Huang et al., 2016; Shakya et al., 2016; Mirabelli et al., 2015; Weichenthal et al., 2011). Effects were not observed in other studies of pulmonary inflammation (Zuurbier et al., 2011a) or lung function decrements (Matt et al., 2016; Zhao et al., 2015; Zuurbier et al., 2011b; Fan et al., 2008). For $PM_{2.5}$ exposures of 1−8 hours, no distinct pattern of association or effect is observed by exposure duration or concentration. Among epidemiologic studies in the U.S., Canada, and Europe conducted near traffic or a steel plant, 1- to 8-hour average $PM_{2.5}$ concentrations with means 8.1−39 $\mu g/m^3$ were linked to respiratory effects in some studies (Mirabelli et al., 2015; Mirowsky et al., 2015; Dales et al., 2013), but not in others (Strak et al., 2012; Weichenthal et al., 2011). Results are inconsistent at concentrations higher than 39 $\mu g/m^3$ as well, but associations were observed in traffic police, adults exercising outdoors, or adults exposed in a transport hub (Huang et al., 2016; Shakya et al., 2016; Kesavachandran et al., 2015; Zhao et al., 2015) with mean 2- to 8-hour average $PM_{2.5}$ concentrations 53−323 $\mu g/m^3$.

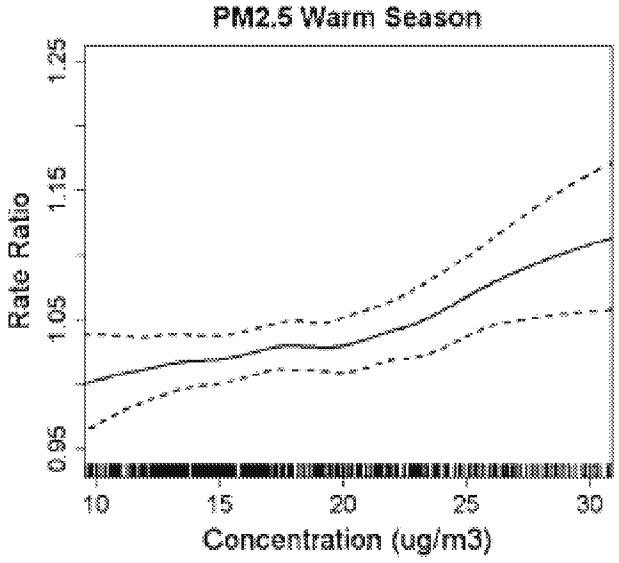
Across the studies evaluated that examined subdaily averaging times and subsequent respiratory effects, the effects tend to be transient. $PM_{2.5}$-associated increases in pulmonary inflammation and oxidative stress (Steenhof et al., 2013; Weichenthal et al., 2011) or decreases in lung function (Mirabelli et al., 2015) often were isolated to immediately or 1 or 2 hours after exposure near traffic, but not 3 to 18 hours after exposure. $PM_{2.5}$ exposure while walking near high-traffic roads and in a forest was associated with eNO 24 hours after exposure (Mirowsky et al., 2015), but lung function decreased only immediately after exposure.

5.1.10.6 Concentration-Response Relationship and Threshold Analyses

At the completion of the 2009 PM ISA, the examination of the PM C-R relationship in epidemiologic studies focused on mortality and cardiovascular outcomes. Recent studies expanded the evaluation of the $PM_{2.5}$ C-R relationship to encompass respiratory-related outcomes, including respiratory-related hospital admissions and ED visits with a focus on examining both the shape of the C-R

curve and whether a threshold exists below which there is no evidence of an effect. Across studies, different analytical methods have been employed to examine the C-R relationship, either explicitly examining the shape of the C-R curve and whether there is evidence of linearity across the full range of $PM_{2.5}$ concentrations, or through cutpoint analyses that examine the risk of a $PM_{2.5}$-related respiratory effect changes within specified ranges of different $PM_{2.5}$ concentrations.

Studies conducted in Atlanta, GA (Strickland et al., 2010), Ontario, Canada (Weichenthal et al., 2016), Dongguan, China (Zhao et al., 2016) and New York, NY (Silverman and Ito, 2010) focused on examining the shape of the $PM_{2.5}$ C-R curve for asthma ED visits or hospital admissions. In Strickland et al. (2010), which focused on pediatric ED visits, a locally weighted scatterplot smoothing (LOESS) C-R analysis provided evidence of a linear C-R relationship for $PM_{2.5}$ in the warm season along the distribution of $PM_{2.5}$ concentrations from the 5th to 95th percentile (Figure 5-19).

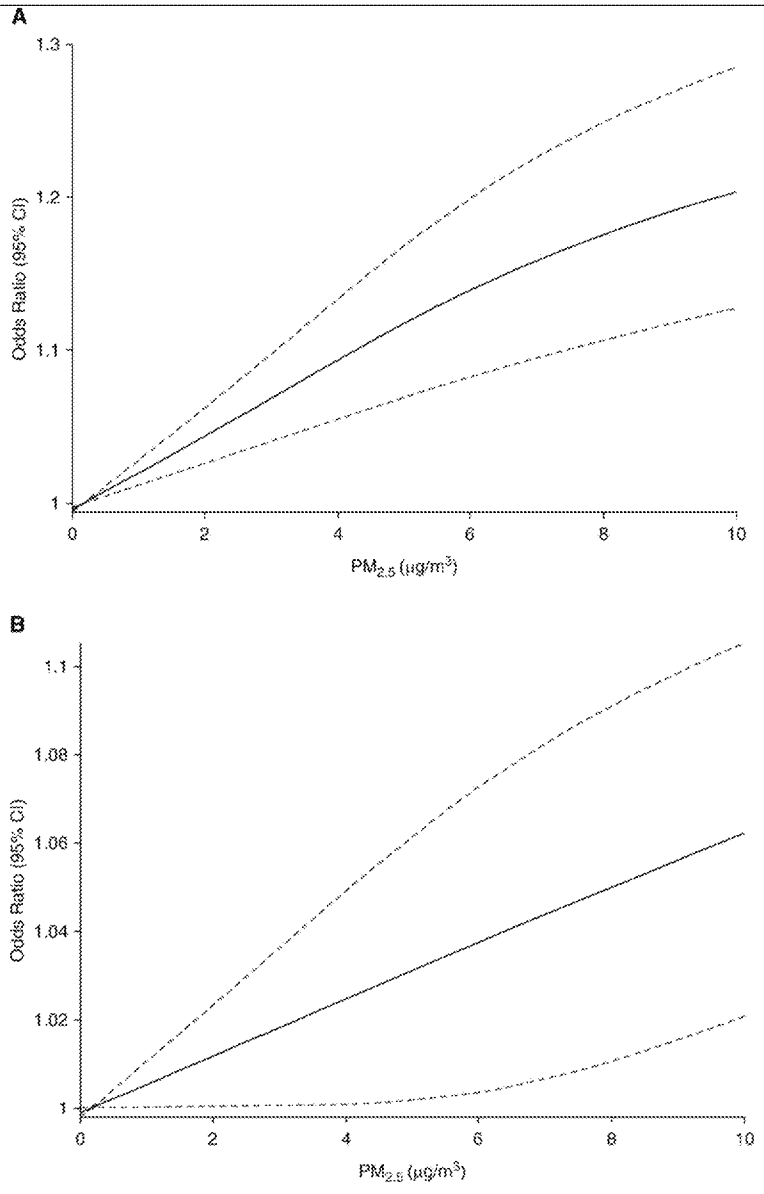


Note: Solid line = smoothed concentration-response estimate. Dashed line = twice-standard error estimates.
Source: Permission pending, Strickland et al. (2010).

Figure 5-19 Concentration-response for associations between 3-day average (lag 0–2) $PM_{2.5}$ concentrations and emergency department (ED) visits for pediatric asthma at the 5th to 95th percentile of $PM_{2.5}$ concentrations in the Atlanta, GA area during the warm season.

Additionally, Weichenthal et al. (2016) examined the C-R relationship for asthma ED visits among children <9 years of age and all ages in 15 Ontario cities in a case-crossover analysis. The authors examined the C-R curve across the range of $PM_{2.5}$ concentrations representing the 95th percentile of the observed difference in lag 0–2 $PM_{2.5}$ concentrations between case and control days, which represented

concentrations ranging from 0–10 μg/m^3, Weichenthal et al. (2016) reported evidence of a linear relationship for both age ranges, but confidence intervals were larger for the all ages analysis (Panel B of Figure 5-20). Evidence of a linear relationship was also observed by Zhao et al. (2016) at $PM_{2.5}$ concentrations much higher than those examined in the U.S. and Canadian studies. Although the results of Strickland et al. (2010), Weichenthal et al. (2016), and Zhao et al. (2016) are informative for assessing the shape of the C-R curve, the authors did not empirically examine alternatives to linearity.

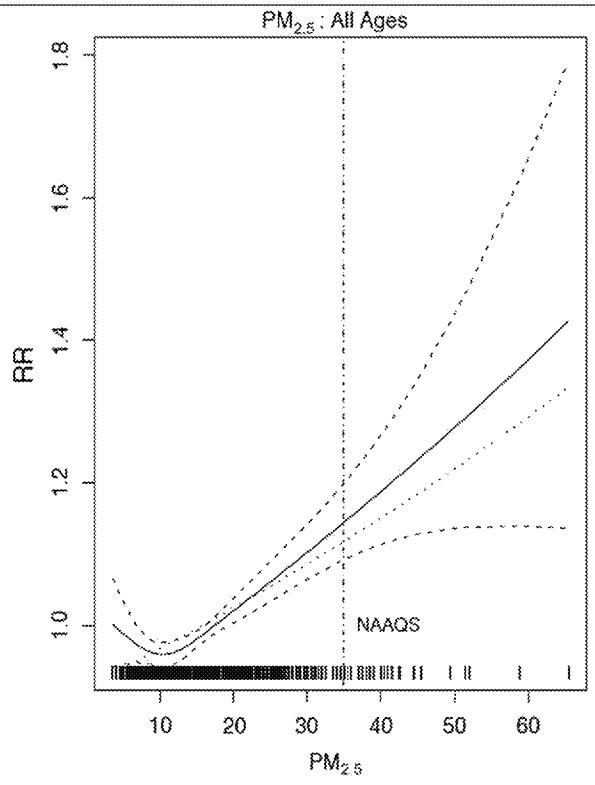


Note: Solid lines represent point estimates, and dashed lines represent 95% confidence intervals.
Source: Permission pending, Weichenthal et al. (2016).

Figure 5-20 Concentration-response curve for lag 0–2-day $PM_{2.5}$ concentrations and asthma emergency department (ED) visits for children (<9 years old) (Panel A) and all ages (Panel B).

Silverman and Ito (2010) assessed whether there was evidence for deviations in linearity for the relationship between short-term $PM_{2.5}$ exposure at lag 0–1 day and asthma hospital admissions by including a smooth function of lag 0–1-day ozone concentrations in the model. When comparing the results from the function including natural splines to account for potential deviations in linearity to a

linear fitted model, the authors observed no evidence that a nonlinear model better represents the C-R relationship (Figure 5-21).



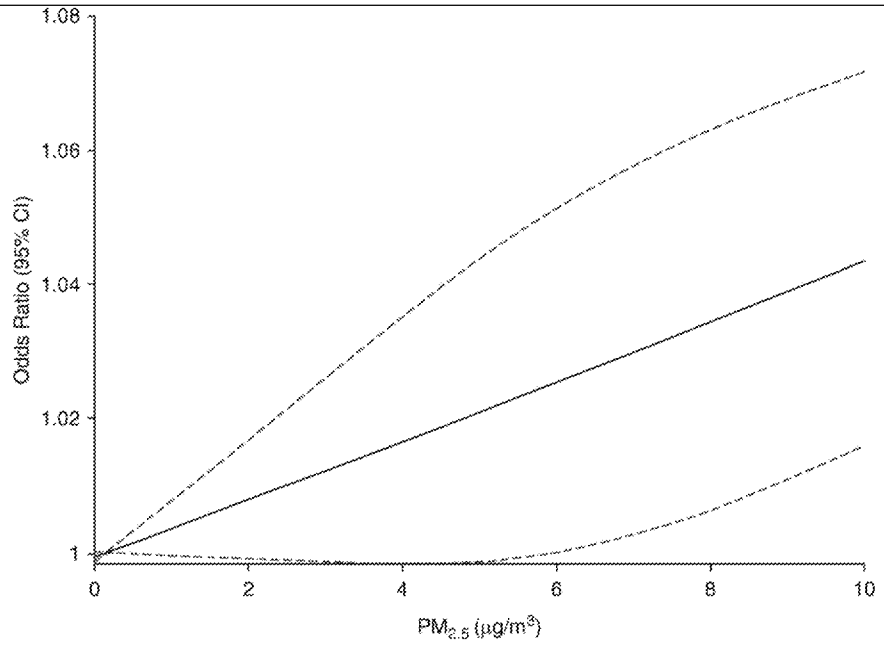
Note: Solid lines = smoothed fitted data, large dashed lines = 95% confidence intervals, short dashed lines = linear fitted data, vertical solid line = current 24-hour average $PM_{2.5}$ NAAQS.

Source: Permission pending, Silverman and Ito (2010).

Figure 5-21 Estimated relative risks (RRs) for short-term $PM_{2.5}$ exposure and asthma hospital admissions at lag 0–1 adjusted for ozone at lag 0–1 allowing for a possible nonlinear relationship in New York, NY.

Additional studies focusing on respiratory-related hospital admissions also examined whether there was evidence of linearity and reported results consistent with the studies focusing on asthma hospital admissions and ED visits.

Weichenthal et al. (2016) also examined the C-R relationship for COPD ED visits in 15 cities in Ontario, Canada. Using the same approach to examine the C-R curve for asthma ED visits, in the COPD analysis the authors reported evidence of a linear relationship (Figure 5-23). The C-R analyses conducted by Weichenthal et al. (2016) and Stafoggia et al. (2013) are also supported by Zhao et al. (2016) in a study conducted in Dongguan, China that demonstrated a linear relationship, albeit at $PM_{2.5}$ concentrations much higher than those examined in the U.S. and Canadian studies.



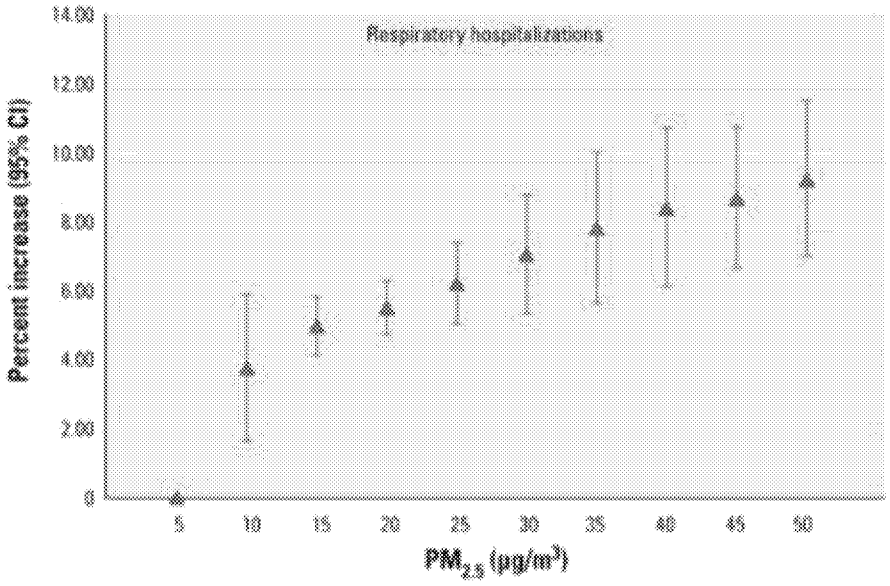
Source: Permission pending, Weichenthal et al. (2016).

Figure 5-22 Concentration-response relationship between 0–2 day mean $PM_{2.5}$ concentrations and chronic obstructive pulmonary disease (COPD) emergency department (ED) visits in Ontario, Canada.

While the studies discussed up to this point have focused specifically on the shape of the C-R curve across the full range of $PM_{2.5}$ concentrations in their respective study locations, other studies focused analyses on specific ranges of $PM_{2.5}$ concentrations to examine whether there is evidence of deviations in linearity. In a study conducted in Detroit, MI, Li et al. (2011) examined whether there is evidence of a nonlinear C-R relationship between air pollutants and pediatric asthma ED visits. Associations with $PM_{2.5}$ were examined in both a time-series and time-stratified, case-crossover study design assuming (1) a linear relationship and (2) a nonlinear relationship starting at 12 $\mu g/m^3$ (i.e., the maximum likelihood estimate within the 10th to 95th percentile concentration where a change in linearity

may occur), which was identified as somewhere in the range of the 35th to 49th percentile of $PM_{2.5}$ concentrations for the time-series and case-crossover analysis, respectively. It is important to note that in the analysis that assumed a nonlinear relationship, the authors did not assume zero risk below the inflection point, which would represent a true threshold. The focus of the analysis by Li et al. (2011) was on identifying whether risk increased above that observed in the linear models at $PM_{2.5}$ concentrations above 12 $\mu g/m^3$. In the analyses assuming linearity, the authors examined single-day lags of 3 and 5 days and multiday lags of 0–2 and 0–4 days. Positive associations were observed for all lags examined and were relatively consistent across models, with the strongest association, in terms of magnitude and precision, for a 0–4-day lag (time series: RR = 1.03 [95% CI: 1.00, 1.07]; case-crossover: OR = 1.04 [95% CI: 1.01, 1.07]). In the models that examined whether there was evidence of nonlinearity, the authors reported larger risk estimates for $PM_{2.5}$ concentrations above 12 $\mu g/m^3$, indicating potential nonlinearity in the $PM_{2.5}$-asthma hospital admissions and ED visit relationship (time series: RR = 1.07 [95% CI: 1.03, 1.11); case-crossover: OR = 1.06 (95% CI: 1.03, 1.09].

Instead of examining the association between short-term $PM_{2.5}$ exposure and asthma hospital admissions and between short-term $PM_{2.5}$ exposure and ED visits at one point along the distribution of $PM_{2.5}$ concentrations as was done by Li et al. (2011), Strickland et al. (2010), in Atlanta, GA, Gleason et al. (2014), in New Jersey, and Stafoggia et al. (2013) in eight European cities examined whether the associations varied across defined cutpoints along the distribution of $PM_{2.5}$ concentrations. Both studies provide some evidence indicating potential nonlinearity in the C-R relationship. In a quintile analysis of lag 0–2-day $PM_{2.5}$ concentrations, Strickland et al. (2010) examined whether risk estimates increased across the quintiles in both the warm and cold season when compared to the 1st quintile (i.e., <10 $\mu g/m^3$). Results were null across all quintiles for the cold season except the highest quintile (i.e., 23.8 ≤ 65.8) (RR = 1.05 [95% CI: 0.99, 1.11]). However, in the warm season, there was evidence of an increase in the magnitude of the association from the 3rd to 5th quintiles, ranging from 1.01–1.05, although confidence intervals were wide. Gleason et al. (2014) which also focused on lag 0–2 $PM_{2.5}$ concentrations, similarly reported a positive association for the highest quintile (i.e., 16.9–47.2 $\mu g/m^3$) (OR = 1.04 [95% CI: 0.98, 1.10]). However, the authors observed no evidence of an association for $PM_{2.5}$ concentrations in the range of the 3rd and 4th quintiles (i.e., 8.5–16.8 $\mu g/m^3$), but reported the association largest in magnitude for the 2nd quintile (i.e., 6.1–8.5 $\mu g/m^3$) (OR = 1.06 [95% CI: 1.01, 1.12]). Instead of focusing on quintiles, Stafoggia et al. (2013) examined associations between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions across various concentration ranges relative to 5 $\mu g/m^3$. The authors first combined results across each individual city by incorporating a natural spline with two equally spaced knots and then applying a metasmoothing approach to develop a combined result across the cities. As demonstrated in Figure 5-23, Stafoggia et al. (2013) report positive associations across each of the cut-points evaluated indicating no evidence of a threshold.



Source: Permission pending, Stafoggia et al. (2013).

Figure 5-23 Cut-point analysis examining the association between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions, lag 0–5, relative to 5 µg/m^3.

Across the studies that examined the shape of the C-R curve, there is some evidence for a linear relationship for short-term $PM_{2.5}$ exposure and both respiratory disease and asthma hospital admissions and ED visits. However, complicating the interpretation of these results is both the lack of thorough empirical evaluations of alternatives to linearity as well as the results from cutpoint analyses that provide some potential indication for nonlinearity in the relationship between short-term $PM_{2.5}$ exposure and respiratory disease and asthma hospital admission and ED visits.

5.1.11 $PM_{2.5}$ Components and Sources and Respiratory Effects

While many PM components are associated with a range of health effects, the 2009 PM ISA concluded that there was "not yet sufficient evidence to allow differentiation of those [components] or sources that more closely related to specific health outcomes" compared to $PM_{2.5}$ mass (U.S. EPA, 2009). For respiratory effects, studies available at the completion of the 2009 PM ISA that examined PM components were few, and the overall evidence linking increases in respiratory effects with short-term exposure to $PM_{2.5}$ components and sources was less consistent than for other health outcomes (i.e., cardiovascular disease and mortality). However, there was some evidence of positive associations between respiratory ED visits and decrements in lung function with sulfate. In addition, several PM sources (i.e., crustal/soil/road dust and traffic) were associated with increased respiratory symptoms in

children with asthma and decreased PEF in adults with asthma. Generally, studies that evaluated individual PM components with respiratory morbidity and mortality observed inconsistent results, with limited evidence from a few studies that evaluated several metals (i.e., Cu, Pb, Zn) as well as OC were associated with respiratory health effects.

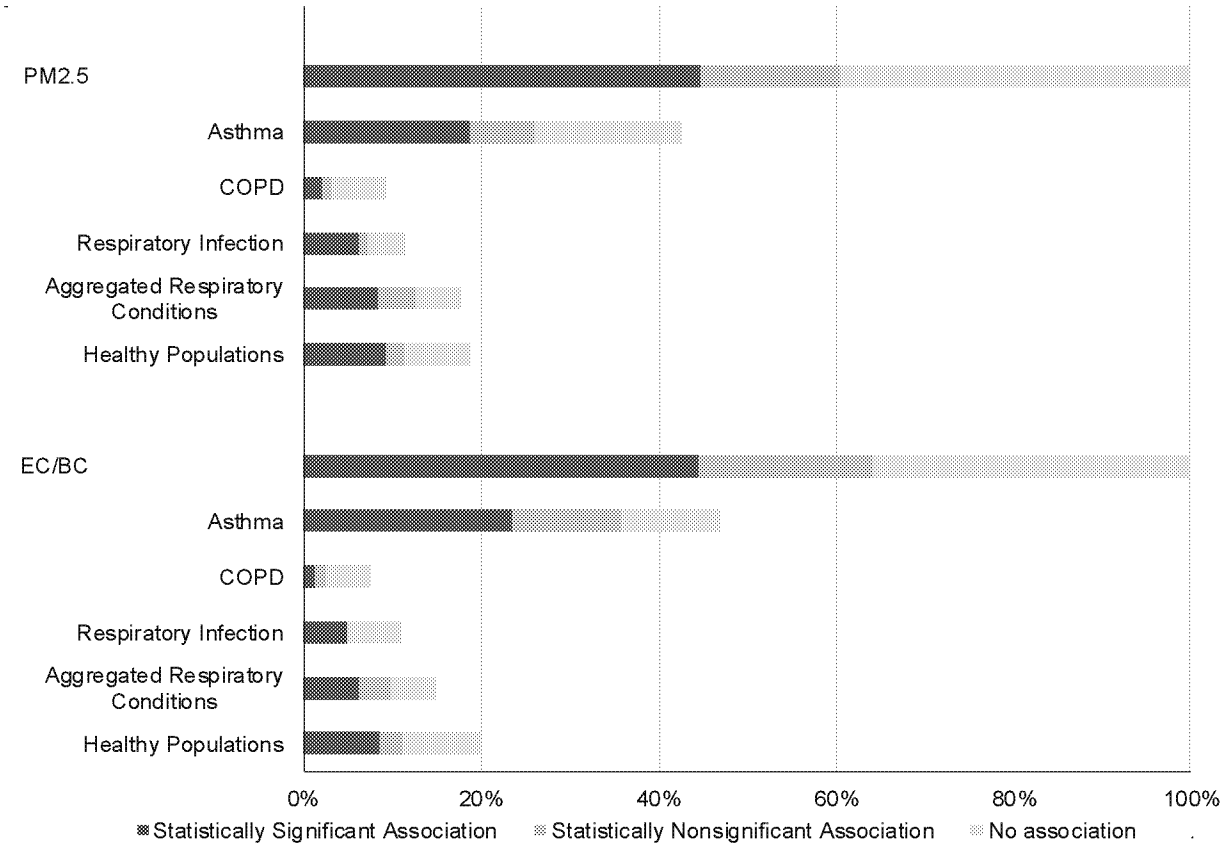
To provide a thorough and consistent evaluation of the evidence with respect to whether a component(s) or source(s) are more strongly related to respiratory effects than $PM_{2.5}$ mass, the evidence is organized by component or source and discussed in the context of associations with $PM_{2.5}$ mass. Additionally, the evidence for components and sources is evaluated in the context of broad health outcome categories, allowing for an integration of evidence related to specific outcomes (e.g., asthma exacerbation). The examination of the relationship between $PM_{2.5}$ components and respiratory effects can generally be divided into two types of analyses: (1) those that examine whether specific components modify the $PM_{2.5}$-respiratory effects association, or (2) those that examine whether an individual component is associated with respiratory effects and potentially a better indicator of PM toxicity compared to PM mass. Although approach 1 is considered one of the techniques used to assess component toxicity as detailed in Mostofsky et al. (2012) these studies are often used to examine heterogeneity in $PM_{2.5}$-respiratory effect risk estimates. As a result, the focus of this section is on population-level epidemiologic studies using those techniques that fall under approach 2, which includes assessing $PM_{2.5}$ component effect by: component concentration; component proportion; component concentration adjusted for $PM_{2.5}$ mass; component residual; or $PM_{2.5}$ residual (Mostofsky et al., 2012).

This section summarizes the evidence evaluating associations between individual components or sources and asthma exacerbation, respiratory infection, or respiratory effects in healthy populations in the context of associations between those respiratory effects and $PM_{2.5}$ mass. EC/BC was the component most often evaluated in studies of respiratory morbidity, and asthma exacerbations were the respiratory effect most commonly examined. Generally, some studies report positive associations between some components and sources and various respiratory health outcomes, though the consistency and coherence of this evidence varies across components and sources. For example, recent studies examined exposure to the EC/BC component of $PM_{2.5}$ and observed consistent associations with indicators of asthma exacerbation in children, though the associations were similar to those observed with $PM_{2.5}$ exposure. Expanded results for NO_3^- and $PM_{2.5}$ from road dust are inconsistent across the array of respiratory outcomes as is new information on PAHs and oxidative potential of $PM_{2.5}$. Overall, associations with respiratory effects are not more clearly linked to a specific PM component or source compared with $PM_{2.5}$ total mass, and within-study comparisons do not show a consistent difference in association between $PM_{2.5}$ and a particular component or source. The evidence for $PM_{2.5}$ components and sources are detailed below.

5.1.11.1 Elemental and Black Carbon

A large body of recent studies consistently links short-term increases in EC/BC concentration with respiratory effects, with the most studies examining asthma-related effects in children. Studies that observed positive associations between exposure to EC/BC and asthma-related effects in children also observed similar associations with $PM_{2.5}$ mass (Figure 5-24). For EC/BC, results are coherent among asthma ED visits, asthma symptoms, and pulmonary inflammation in populations with asthma. However, like trends observed for $PM_{2.5}$ mass, EC/BC associations with lung function are inconsistent. Neither EC/BC nor $PM_{2.5}$ is consistently associated with COPD exacerbation, and the evidence for EC/BC associations with respiratory infection, aggregated respiratory conditions, or respiratory effects in healthy populations is limited and inconsistent. Within most (Sarnat et al., 2015; Winquist et al., 2014b; Kim et al., 2012) but not all (Xiao et al., 2016) U.S. studies, EC was associated with effects related to asthma but not COPD or respiratory infection. Across respiratory effects, there is generally no difference in the pattern or consistency of associations between EC/BC and $PM_{2.5}$ (Figure 5-24).

Most studies associated respiratory effects with both $PM_{2.5}$ and EC/BC, though some showed associations with only one or the other. Many results point to similar magnitude of association for EC/BC and $PM_{2.5}$, often presented per IQR increase in concentration. Some studies estimated larger effects for EC/BC; others estimated larger effects for $PM_{2.5}$. Respiratory effects were associated with EC/BC in cities across regions of the U.S.; no pattern in the presence of an association for EC/BC or the magnitude relative to $PM_{2.5}$ is discerned by geographic location. In the nationwide U.S. Medicare population, EC was not associated with hospital admissions for all respiratory diseases combined (Levy et al., 2012). These results add 2 years to those of Peng et al. (2009a) (2000−2008 vs. 2000−2006), who reported an association with EC. The recent analysis by Levy et al. (2012) indicated the likelihood of greater risk for EC than $PM_{2.5}$ in the East. For locations showing similar magnitude associations for EC/BC and $PM_{2.5}$, correlations ranged 0.23−0.83. Across these studies, no pattern is observed for EC/BC by its correlation with $PM_{2.5}$. Most studies were conducted across seasons, so a pattern of association for EC by season in not discernable. Where stratified by season, EC/BC and $PM_{2.5}$ associations were similar in the same season. Warm season associations with asthma ED visits are indicated in Atlanta, GA and St. Louis, MO (Winquist et al., 2014b; Strickland et al., 2010), and cold season associations with pneumonia hospital admissions are indicated in Boston, MA (Zanobetti and Schwartz, 2006).



BC = black carbon, EC = elemental carbon, $PM_{2.5}$ = particulate matter with nominal mean aerodynamic diameter ≤2.5 µm.
Note: Colored bars indicate the proportion of those studies observing statistically significant positive associations, positive associations, null associations, negative associations, and statistically significant negative associations.

Figure 5-24 Associations for $PM_{2.5}$ total mass and elemental or black carbon with respiratory effects by outcome group.

Potential measurement error is an important consideration in drawing inferences from associations observed with EC/BC and in in comparing the effects relative to $PM_{2.5}$. Consistent with the contribution of local motor vehicle emissions to EC/BC and regional sources to $PM_{2.5}$, some studies indicated greater spatiotemporal variability in concentrations of EC/BC than $PM_{2.5}$. Both BC and $PM_{2.5}$ were highly correlated between two schools in Ciudad Juarez, Mexico ($r = 0.85$ for BC, $r = 0.93$ for $PM_{2.5}$) (Sarnat et al., 2012) but not between schools in El Paso, TX, where the correlation was moderate for BC and high for $PM_{2.5}$ ($_r = 0.60$ for BC, $_r = 0.89$ for $PM_{2.5}$) (Greenwald et al., 2013; Zora et al., 2013). In New York, NY, correlations between BC and $PM_{2.5}$ were moderate, and varied across schools ($_r = 0.47–0.68$) (Patel et al., 2010). For these schools that varied in proximity to or intensity of traffic, the school-based EC/BC and $PM_{2.5}$ may have had more comparable exposure error than measurements at

central site monitors. Across studies, concentrations of EC/BC measured at schools were associated with larger increases in symptoms and pulmonary inflammation and larger decreases in lung function among children with asthma (Greenwald et al., 2013; Patel et al., 2013; Zora et al., 2013; Sarnat et al., 2012; Spira-Cohen et al., 2011; Patel et al., 2010).

The associations for respiratory effects and EC or $PM_{2.5}$ measured from personal exposures likely have comparable exposure error. Total personal EC concentrations, but not $PM_{2.5}$ concentrations, were associated with asthma-related effects among children in New York, NY (Spira-Cohen et al., 2011), whereas the opposite was observed for children in Los Angeles, CA (Delfino et al., 2008). One explanation could be variation in sources, for example, indoor exposures. EC and $PM_{2.5}$ were more highly correlated for ambient ($r = 0.51$) than personal measurements ($r = 0.22, 0.43$). Personal EC was weakly correlated with school EC in New York, NY ($r = 0.27$) and uncorrelated with central site EC in Los Angeles, CA ($r = -0.01$). The relative impact of personal ambient $PM_{2.5}$ and EC exposures also varied for adults (mostly healthy populations) exposed for 2–5 hour in high- and low-traffic locations. Some studies estimated larger effects for $PM_{2.5}$, and correlations with EC/BC were low ($r = 0.29, 0.39$) (Kubesch et al., 2015; Mirabelli et al., 2015; Mirowsky et al., 2015). Other studies estimated similar effects for EC/BC and $PM_{2.5}$ (Huang et al., 2016; Steenhof et al., 2013; Strak et al., 2012; Zuurbier et al., 2011b).

Associations with asthma-related hospital admissions and ED visits are generally the same for EC/BC and $PM_{2.5}$ measured at central site monitors. Effect estimates were similar per IQR increases in EC and $PM_{2.5}$ during 1993–2001 (Strickland et al., 2011; Strickland et al., 2010) but stronger for $PM_{2.5}$ in later years (2002–2010) (Strickland et al., 2014). For both EC and $PM_{2.5}$, similar effects were estimated when assigning exposure using concentrations at a monitor in the city center and those averaged across monitors by weighting by population density. The representativeness of EC and $PM_{2.5}$ metrics is supported by high correlations between exposure assessment methods ($r = 0.96$ for $PM_{2.5}$, 0.80 for EC) and the high density of asthma ED visits in the city center. There are greater uncertainties in comparisons in St. Louis, MO showing larger or similar increases in asthma ED visits for $PM_{2.5}$ than EC/BC when a single monitor was used (Sarnat et al., 2015; Winquist et al., 2014b). EC concentrations were spatiotemporally variable relative to $PM_{2.5}$ (median intersite $r = 0.88$ for $PM_{2.5}$ and 0.47 for EC).

Recent statistical analyses support an association for EC/BC independent of $PM_{2.5}$. Robust associations for EC are observed after adjusting for the non-EC portion of $PM_{2.5}$, which made up 96% total mass (Sarnat et al., 2012) or adjusting for the residuals from a model regressing EC with $PM_{2.5}$ (Basagaña et al., 2015). The latter also showed an association for $PM_{2.5}$. In copollutant models, associations for EC/BC persist when adjusted for $PM_{2.5}$, but associations for $PM_{2.5}$ adjusted for EC/BC were attenuated in some cases (Samoli et al., 2016c; Lin et al., 2011). A role for EC in modifying $PM_{2.5}$ effects is unclear based on contrasting results in the Medicare population. The $PM_{2.5}$ association with aggregated respiratory-related hospital admissions or ED visits increased as the EC fraction of long-term average $PM_{2.5}$ increased when assessed in 106 U.S. counties for 2000–2005 (Bell et al., 2009b) but was unaffected when assessed in 26 cities for 2000–2003 (Zanobetti et al., 2009). Across the 26 cities, EC

comprised 2−14% of total $PM_{2.5}$ mass. Other studies showed no consistent difference in association between EC and $PM_{2.5}$ in locations where EC made up 4−8% of $PM_{2.5}$ (Basagaña et al., 2015; Sarnat et al., 2015; Bell et al., 2014; Winquist et al., 2014b; Spira-Cohen et al., 2011; Peng et al., 2009a). Whether EC/BC has an effect independent of traffic-related copollutants is still uncertain. Correlations were high with UFP (r = 0.84−0.86) and wide-ranging with NO_2 or NO_X (r = 0.36−0.76). In copollutant models examined only with NO_2 or NO_X, associations for personal ambient EC were robust in some cases (Strak et al., 2012) but attenuated in others (Steenhof et al., 2013; McCreanor et al., 2007). Among children in New York, NY, associations for total personal EC were robust to adjustment for school NO_2 (Spira-Cohen et al., 2011), but potential differential measurement error limits inferences from the results. A similar uncertainty applies to results for asthma ED visits in Georgia not indicating synergistic interactions for EC with the highly correlated NO_2, CO, and OC (Xiao et al., 2016). The fused-CMAQ model's predictive capacity of EC, CO, and OC concentrations was mediocre (cross-validation R^2 = 0.53−0.54).

Overall, there is generally no difference in the pattern or consistency of associations between EC/BC and $PM_{2.5}$ across respiratory effects. A large body of recent studies that consistently observed positive associations between exposure to EC/BC and respiratory effects also observed similar associations with $PM_{2.5}$ mass. These results continue to support the conclusion in the 2009 PM ISA that there is "not yet sufficient evidence to allow differentiation of those [components] or sources that more closely related to specific health outcomes" compared to $PM_{2.5}$ mass (U.S. EPA, 2009).

5.1.11.2 Organic Carbon

In contrast with studies characterized in the 2009 PM ISA, recent studies consistently report a positive association of OC with asthma-related hospital admissions, ED visits, symptoms, and pulmonary inflammation but not lung function decrements. Recent results from a limited number of studies demonstrate consistent positive associations between OC exposure and aggregated respiratory-related diseases but not COPD exacerbation, respiratory infection, or respiratory effects in healthy population. Across these studies, the consistency and magnitude of respiratory effect associations are generally similar for OC and $PM_{2.5}$, and these studies report moderate to high correlations between OC and $PM_{2.5}$ (r = 0.51−0.87) (Krall et al., 2016; Xiao et al., 2016; Basagaña et al., 2015; Jones et al., 2015; Sarnat et al., 2015; Kim et al., 2012) and a large contribution of OC to total $PM_{2.5}$ mass [Section 2.5.1.1.6 and 11 and 21% in (Jones et al., 2015; Sarnat et al., 2015)]. In exception to most results, a recent analysis of the U.S. Medicare population indicates greater risk of hospital admission for respiratory infection for OC than $PM_{2.5}$ (Levy et al., 2012).

Like $PM_{2.5}$, OC was associated with respiratory effects among people of all ages or children in locations across U.S. regions. During 2000−2008, OC was linked to hospital admissions for respiratory infection in 98 eastern but not 21 western U.S. counties (Levy et al., 2012). Risk estimates for $PM_{2.5}$ with

hospital admissions for COPD plus respiratory infection during 2000–2003 did not vary by the long-term average OC to $PM_{2.5}$ ratio, which ranged 0.10 to 0.99 across 26 cities and four seasons (Zanobetti et al., 2009). Both OC and $PM_{2.5}$ show associations in the cold and warm season, but few seasonal analyses were conducted. Except for pneumonia, associations for OC and $PM_{2.5}$ are larger in the warm season in U.S. locations (Jones et al., 2015; Winquist et al., 2014b; Strickland et al., 2010).

The lack of clear differences in associations between OC and $PM_{2.5}$ is observed across exposure assessment methods, including concentrations at central site monitors in Atlanta, GA where OC and $PM_{2.5}$ similarly showed spatiotemporal homogeneity ($r = 0.96$ for $PM_{2.5}$, 0.89 for OC between a monitor in the city center and a population-weighted average) (Strickland et al., 2011) and St. Louis, MO where OC was more variable than $PM_{2.5}$ (median intersite $r = 0.43$ for OC, 0.88 for $PM_{2.5}$) (Sarnat et al., 2015). Results did not consistently differ between OC and $PM_{2.5}$ for weakly correlated ($r = 0.26$) total personal exposures of children with asthma (Delfino et al., 2008; Delfino et al., 2006) and moderately to highly correlated ($r = 0.40–0.79$) personal ambient exposures of adults during 2 or 5 hours spent in high- or varying-traffic locations (Mirabelli et al., 2015; Mirowsky et al., 2015; Strak et al., 2012). In addition to the uncertainty of associations of OC that are independent of the effects of $PM_{2.5}$ mass, it is also unclear if the association for OC with respiratory effects is independent of moderately correlated NO_2 or EC/BC ($r = 0.44–0.51$ with NO_2, 0.53–0.64 with EC) given that no studies examined confounding.

5.1.11.3 Secondary $PM_{2.5}$—Sulfate, Nitrate, Ammonium

Several recent studies add to the limited body of evidence in the 2009 PM ISA for associations of SO_4^{2-} and asthma exacerbation, and several recent studies contribute evidence to characterize the associations between NO_3^-, and ammonium (NH_4^+) and respiratory effects (Figure 5-25). Evidence for effects on asthma exacerbation are generally more consistent than associations for other respiratory outcomes. In most locations, results are similar between $PM_{2.5}$ and SO_4^{2-} or NH_4^+ in direction and magnitude of association. In the U.S., Europe, and Asia, there was consistent evidence of positive associations for SO_4^{2-}, NH_4^+, and NO_3^- (Wang and Lin, 2016; Jones et al., 2015; Steenhof et al., 2013; Kim et al., 2012; Atkinson et al., 2010). However, in some instances, associations were observed with NO_3^- but not SO_4^{2-} (Ostro et al., 2016; Mann et al., 2010), or associations were observed with SO_4^{2-} but not NO_3^- (Sarnat et al., 2015; Darrow et al., 2014; Strickland et al., 2014). Analyses of the U.S. Medicare population did not report consistently positive associations for SO_4^{2-} or NO_3^- across respiratory effects. For 2000–2008, hospital admissions for respiratory infection were not associated with SO_4^{2-} or NO_3^- in the east or west (Levy et al., 2012). For 2000–2006, hospital admissions for respiratory infection and COPD combined were associated with SO_4^{2-} not NO_3^- (Peng et al., 2009a).

For U.S. locations, associations for SO_4^{2-}, NO_3^-, and NH_4^+ tends to follow their relation to total $PM_{2.5}$ mass. Where associations were observed for SO_4^{2-} but not NO_3^-, $PM_{2.5}$ was highly correlated with SO_4^{2-} ($r = 0.74–0.81$) not NO_3^- ($r = 0.02–0.45$) (Sarnat et al., 2015; Darrow et al., 2014; Strickland et al.,

2014; Peng et al., 2009a). The converse was observed in California (r for $PM_{2.5}$ = 0.9 with NO_3^- and <0.5 with SO_4^{2-}) (Ostro et al., 2009). Where associations were observed with SO_4^{2-} and NO_3^-, both were highly correlated with $PM_{2.5}$ (r = 0.68–0.97 for SO_4^{2-}, 0.51–0.82 for NO_3^-) (Wang and Lin, 2016; Jones et al., 2015; Kim et al., 2012; Atkinson et al., 2010). The few available seasonal analyses show higher concentrations of SO_4^{2-} and NH_4^+ in the warm season and of NO_3^- in the cold season.

Analyses of effect measure modification also do not clearly show that SO_4^{2-}, NO_3^-, or NH_4^+ influences $PM_{2.5}$-associated respiratory effects. Consistent with previous findings (Bell et al., 2009b), recent results in the Medicare population show no clear difference in $PM_{2.5}$-associated respiratory hospital admissions by the ratio of SO_4^{2-}, NO_3^-, or NH_4^+ to $PM_{2.5}$ in New York State (Jones et al., 2015) and low probability that risk for SO_4^{2-} or NO_3^- is greater than that for $PM_{2.5}$ in the U.S. overall (Levy et al., 2012). An independent association for SO_4^{2-} is not clearly indicated with adjustment for the non-SO_4^{2-} portion of $PM_{2.5}$ in St. Louis, MO (Sarnat et al., 2015) or residuals from a model regressing $PM_{2.5}$ on SO_4^{2-} concentrations in Europe (Basagaña et al., 2015). In California, the association for NO_3^- was robust to adjustment for a factor of traffic-related $PM_{2.5}$ components (Ostro et al., 2016).

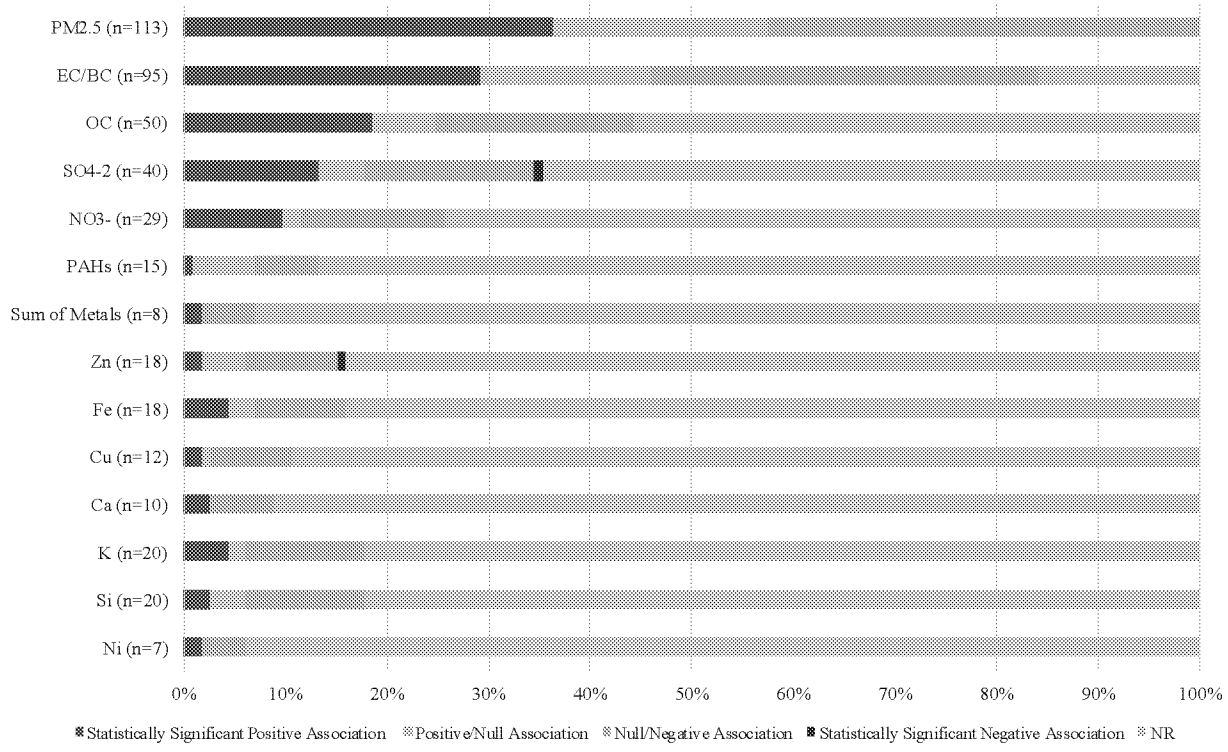
5.1.11.4 Metals

Compared with $PM_{2.5}$ mass, short-term exposures to metal components of $PM_{2.5}$ are inconsistently associated with respiratory effects (Figure 5-25). In the expanded body of recent studies, relatively few observed associations with a metal that differed substantially from the association with $PM_{2.5}$ mass (Ferreira et al., 2016; Bell et al., 2014; Strak et al., 2012; Hong et al., 2010). Most studies that included a metal component of $PM_{2.5}$ observed an association with some metal, and studies that examined numerous metals observed an association with multiple metals. However, findings are inconsistent for any individual metal or the sum of metals. Fe, Zn, Cu, Ca, K, and Si are most studied, and many associations are positive for Fe or Zn with indicators of asthma exacerbation (Prieto-Parra et al., 2017; Mirabelli et al., 2015; Hong et al., 2010; Sinclair et al., 2010; Gent et al., 2009; Ostro et al., 2009). Results are mostly null for Al, Mn, Pb, As, Se, Br, Ti, and V, but associations for V tend to be similar to those for Ni (Basagaña et al., 2015; Bell et al., 2014).

Neither the percentage contribution metals make to $PM_{2.5}$ mass nor the correlation between metal and $PM_{2.5}$ mass concentrations affected the pattern of associations between metal components and respiratory effects. Where metals comprised less than 1% of $PM_{2.5}$, associations with respiratory effects were observed in Bell et al. (2014), but not Sarnat et al. (2015). The range of correlations between metals and $PM_{2.5}$ (r = 0.25–0.63) did not clearly differ between studies that observed (Krall et al., 2016; Basagaña et al., 2015; Ostro et al., 2009) and did not observe (Basagaña et al., 2015; Sarnat et al., 2015) positive associations with metals. Few seasonal analyses were conducted to assess a pattern of association. Previous U.S.-wide analyses indicate that the $PM_{2.5}$ association with respiratory hospital admissions varies across cities depending on the percentage of Na, Ca, Ni or V (Bell et al., 2009b;

Zanobetti et al., 2009), with (Bell et al., 2009b) indicating effect modification by Ni or V only when New York, NY counties were included. Recent studies confirm a positive association with Ni and V in the Northeast (i.e., Connecticut and Massachusetts) (Bell et al., 2014; Gent et al., 2009).

Ambient concentrations of metals can be spatiotemporally more heterogeneous than $PM_{2.5}$ total mass. In St. Louis, MO, $PM_{2.5}$ but not metals were associated with asthma ED visits, and Fe, Cu, and Zn were variable across monitors (median $r = 0.54$ for Fe, 0.03 for Cu and Zn) (Sarnat et al., 2015). Exposure measurement error could contribute to inconsistent findings for metals. However, personal Fe exposures while driving in a car or in locations with varying traffic levels were inconsistently associated with lung function decrements or increases in pulmonary inflammation (Mirabelli et al., 2015; Strak et al., 2012).



BC = black carbon, Ca = calcium, Cu = copper, EC = elemental carbon, Fe = iron, K = potassium, N = the number of studies evaluating $PM_{2.5}$ mass or components, Ni = nickel, NO_3^- = nitrate, OC = organic carbon, PAH = polycyclic aromatic hydrocarbon, $PM_{2.5}$ = particulate matter with nominal mean aerodynamic diameter ≤2.5 μm, Si = silicon, SO_4^{2-} = sulfate, Zn = zinc.

Note: Colored bars indicate the proportion of those studies observing statistically significant positive associations, positive associations, null associations, negative associations, and statistically significant negative associations.

Figure 5-25 Distribution of associations for all respiratory effects and short-term $PM_{2.5}$ mass and $PM_{2.5}$ components exposure.

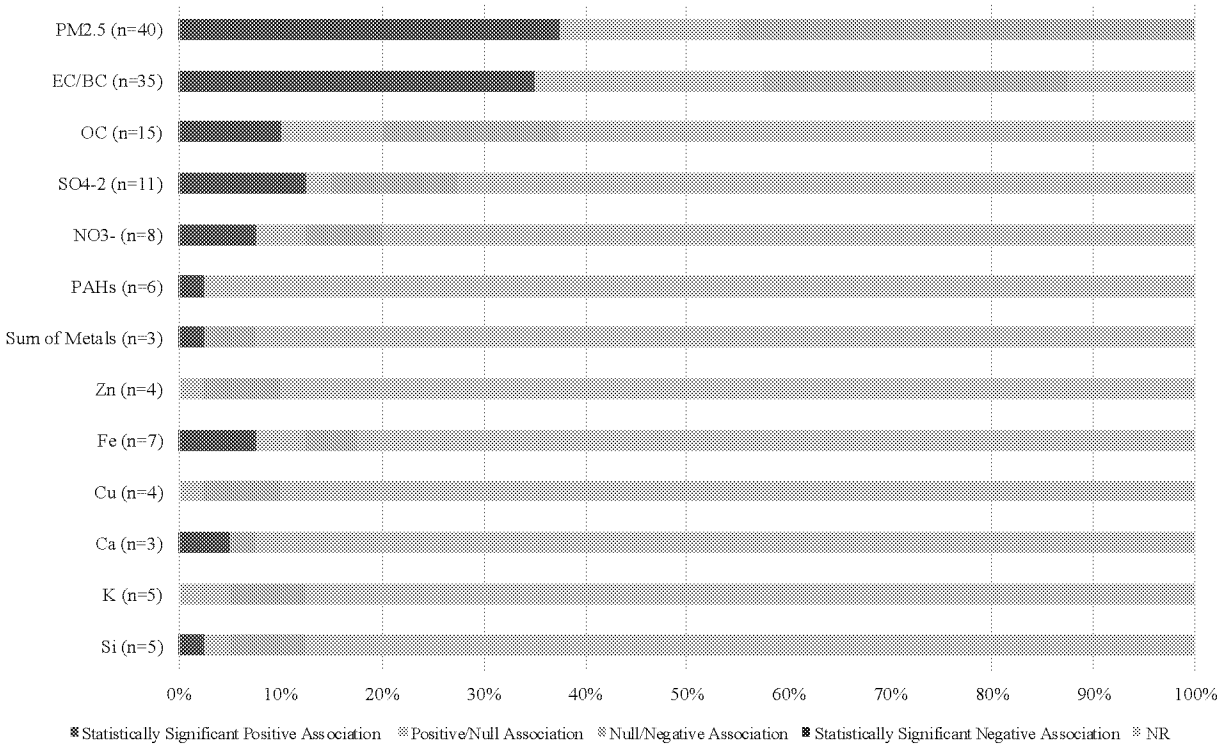
5.1.11.5 Other $PM_{2.5}$ components

Information from a limited number of recent studies links respiratory effects with oxidative potential of $PM_{2.5}$ and chlorine but is inconsistent for polycyclic aromatic hydrocarbons, alkanes, hopanes, and endotoxin. Information is available from a few studies and locations for each of these $PM_{2.5}$ components and for a variety of respiratory effects, with few studies evaluating the same combination of $PM_{2.5}$ component and respiratory effect [e.g., Maikawa et al. (2016); Mirabelli et al. (2015); Sarnat et al. (2015); (Delfino et al., 2013)]. Notably, for the studies examining oxidative potential of $PM_{2.5}$, associations were not observed with total $PM_{2.5}$ mass. Associations for polycyclic aromatic hydrocarbons and alkanes were linked to sources such as traffic or petroleum industries, and associations for endotoxin were linked to farm exposures.

5.1.11.6 Sources of $PM_{2.5}$

A limited number of studies included in the 2009 PM ISA examined associations between respiratory effects and sources of $PM_{2.5}$ (e.g., crustal, soil, road dust, traffic). Several recent studies apportioned $PM_{2.5}$ components into source factors and provide some evidence linking $PM_{2.5}$ from traffic to asthma exacerbation and $PM_{2.5}$ from biomass burning to asthma exacerbation and respiratory infection (Figure 5-25 and Figure 5-26). These respiratory effects also are consistently associated with short-term $PM_{2.5}$ exposures during wildfires. Evidence is inconsistent for $PM_{2.5}$ from dust or soil, and as examined in few studies, oil, salt, long-range transport, and local industry. Results do not appear to depend on the contribution or correlation of a source to $PM_{2.5}$ mass. For example, associations were observed with biomass-related $PM_{2.5}$ comprising 2.8 to 15.8% of mass and showing correlations with $PM_{2.5}$ mass from 0.24 to 0.84. In contrast, long-range transport contributed 30−57% to $PM_{2.5}$ mass. Further, studies that examined numerous sources tended to observe associations with $PM_{2.5}$ with combustion-related activities, specifically traffic and biomass. Some U.S., Canadian, and European studies observed respiratory effects in association with source-specific $PM_{2.5}$ but not with $PM_{2.5}$ mass (Brand et al., 2016; Bell et al., 2014; Alessandrini et al., 2013; Gent et al., 2009), but findings overall are more consistent for $PM_{2.5}$ mass. No clear difference in associations between total $PM_{2.5}$ mass or source-specific $PM_{2.5}$ and respiratory effects is indicated across studies during wildfire and nonwildfire study periods (Kollanus et al., 2016; Salimi et al., 2016; Delfino et al., 2009).

Respiratory effects were associated with $PM_{2.5}$ from motor vehicles or biomass in various U.S. regions, including a study of Atlanta, GA; Birmingham, AL; Dallas, TX; and St. Louis, MO, where $PM_{2.5}$ components were apportioned into similar factors (Krall et al., 2016). Examination of wildfire-related $PM_{2.5}$ mostly focused on the western U.S., including an analysis of 561 counties (Liu et al., 2017), but also included a study focusing on a peat fire in North Carolina (Rappold et al., 2012). No distinct seasonal pattern is discerned for associations with source-specific $PM_{2.5}$, but many wildfires occur during the warm season.



BC = Black carbon, Ca = calcium, Cu = copper, EC = elemental carbon, Fe = iron, K = potassium, N = the number of studies evaluating $PM_{2.5}$ mass or components, NO_3^- = nitrate, OC = organic carbon, PAH = polycyclic aromatic hydrocarbon, $PM_{2.5}$ = particulate matter with nominal mean aerodynamic diameter ≤2.5 μm, Si = silicon, SO_4^{2-} = sulfate, Zn = zinc.

Note: Colored bars indicate the proportion of those studies observing statistically significant positive associations, positive associations, null associations, and negative associations.

Figure 5-26 Associations for asthma exacerbations with $PM_{2.5}$ mass and components.

The results for source-specific $PM_{2.5}$ do not always agree with those for the components that make up the source factors. Respiratory effects are inconsistently associated with dust- or soil-related $PM_{2.5}$, Si, Ca, and Al as well as with salt-related $PM_{2.5}$, Na, and Cl (Section 5.1.11.4). In northeastern U.S. locations, associations were observed with Ni or V but not oil-related $PM_{2.5}$ (Bell et al., 2014; Gent et al., 2009). Similarly, associations are observed with SO_4^{2-} or NO_3^- but inconsistently for factors representing long-range transported $PM_{2.5}$. In New Mexico, no association was observed for $PM_{2.5}$ or for air masses identified as originating from regions in the western U.S. (Rodopoulou et al., 2014). Results agree better for motor vehicle-related $PM_{2.5}$, as evidence also links asthma-related effects to EC (Section 5.1.11.1), OC (Section 5.1.11.2), Zn, and Fe (Section 5.1.11.4), which comprised most motor vehicle source factors. A few studies observed associations with EC/BC or OC but not motor vehicle-related $PM_{2.5}$ (Krall et al., 2016; Bell et al., 2014). The influence of total $PM_{2.5}$ mass or EC/BC does not clearly depend on proximity to traffic. With scripted exposures near roadways, $PM_{2.5}$ and EC/BC are inconsistently associated with

respiratory effects in healthy populations (Section 5.1.7). However, similar inconsistency is observed for children with asthma attending school near major roads (Greenwald et al., 2013; Sarnat et al., 2012). For biomass-related $PM_{2.5}$, results for asthma-related effects tend to correspond with K or OC within studies, but across studies, consistency is observed for OC (Section 5.1.11.2) not K (Section 5.1.11.4).

5.1.11.7 Summary

Generally, some studies report positive associations between some components and sources and various respiratory health outcomes, though the consistency and coherence of this evidence varies across components and sources. Overall, associations with respiratory effects are not more clearly linked to a particular PM component or source compared with $PM_{2.5}$ total mass, and within-study comparisons do not show a consistent difference in association between $PM_{2.5}$ and a specific component or source (Figure 5-25). The majority of studies evaluating $PM_{2.5}$ components examined associations with asthma exacerbation, and these results are presented in Figure 5-26. Some recent studies did not observe increased respiratory effects with $PM_{2.5}$ mass, but did with PM components and sources, typically EC/BC (Section 5.1.11.1) and metals (Section 5.1.11.4). However, in most cases, associations were observed with $PM_{2.5}$ as well as components or sources.

5.1.12 Summary and Causality Determination

The 2009 PM ISA (U.S. EPA, 2009) concluded that a "causal relationship is likely to exist" between short-term $PM_{2.5}$ exposure and respiratory effects (U.S. EPA, 2009).[56] This conclusion was based mainly on epidemiologic evidence demonstrating associations between short-term $PM_{2.5}$ exposure and various respiratory effects. There was more limited evidence from controlled human exposure and animal toxicological studies, which provided coherence and biological plausibility for a subset of epidemiologic findings. Epidemiologic evidence was consistent for COPD exacerbation, respiratory infection, and respiratory mortality and inconsistent for asthma-related hospital admissions and ED visits. However, associations between short-term $PM_{2.5}$ exposure and increased respiratory symptoms and decreases in lung function were observed in children with asthma. Evidence supporting an independent effect of $PM_{2.5}$ on the respiratory system was provided by animal toxicological studies of $PM_{2.5}$ CAPs, which demonstrated changes in some pulmonary function parameters, as well as inflammation, oxidative stress, injury, enhanced allergic responses, and reduced host defenses. Many of these effects have been implicated in the pathophysiology for asthma exacerbation, COPD exacerbation, or respiratory infection. In the few controlled human exposure studies conducted in individuals with asthma or COPD, $PM_{2.5}$ exposure mostly had no effect on respiratory symptoms, lung function, or pulmonary inflammation.

[56] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{2.5}$ concentrations unless otherwise noted.

Short-term $PM_{2.5}$ exposure was not clearly related to respiratory effects in healthy people. For many endpoints the recent epidemiologic evidence is expanded compared with evidence available in the 2009 PM ISA. However, recent controlled human exposure and animal toxicological studies are limited in number. While there are more analyses of potential copollutant confounding indicating that associations are robust to the inclusion of gaseous pollutants, uncertainties remain due to the limited experimental evidence supporting an independent $PM_{2.5}$ effect from controlled human exposure and toxicological studies. The evidence for the relationship between short-term exposure to $PM_{2.5}$ and respiratory effects is summarized in Table 5-18, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

For asthma exacerbation, the key epidemiologic evidence consists of hospital admissions and ED visits. Recent studies strengthen the relationship between asthma exacerbation in children and short-term $PM_{2.5}$ exposure, while, in adults, the relationship continues to be inconsistent. Exposure measurement error related to uncharacterized spatial variability tends to be lower in $PM_{2.5}$ mass concentration compared with other size fractions and species (Section 3.4.2.2). Copollutant models are examined in recent studies of children and people of all ages and add evidence of robust $PM_{2.5}$ associations after adjustment for gaseous copollutants or pollen. Recent studies continue to indicate $PM_{2.5}$-related increases in asthma symptoms and medication use in children, with less consistent evidence for lung function decrements and pulmonary inflammation. In adults, asthma studies with personal 2-hour ambient $PM_{2.5}$ exposures on or near a high-traffic road were associated with lung function decrements. While controlled human exposure studies find little evidence for altered lung function and pulmonary inflammation, animal toxicological studies show enhancement of allergic inflammation, other allergic responses, and airway remodeling in animal models of allergic airway disease. These results provide coherence with and biological plausibility for epidemiologic findings of allergic asthma, the most common phenotype in children. Overall, several well-conducted epidemiologic studies with total personal, residential outdoor, and school outdoor $PM_{2.5}$ measurements show associations with asthma-related effects.

Table 5-18 Summary of evidence for a likely to be causal relationship between short-term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Asthma exacerbation			
Consistent epidemiologic evidence from multiple, high-quality studies at relevant $PM_{2.5}$ concentrations	Increases in asthma-related hospital admissions and ED visits in children, and all ages combined in studies conducted in the U.S. and Canada.	Section 5.1.2.1.1 Section 5.1.2.1.2	7.9–12.9 µg/m^3 7.1–19.2 µg/m^3
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	Expanded examination of potential copollutant confounding for asthma-related hospital admissions and ED visits in recent studies, with evidence that associations remain robust in models with gaseous pollutants. No studies provide copollutant model results with $PM_{10-2.5}$. When reported, correlations with gaseous copollutants were primarily in the low to moderate range ($r < 0.7$).	Section 5.1.10.1	
Coherence in epidemiologic studies across the continuum of effects	Panel studies in children with asthma provide support for asthma exacerbation in children with consistent associations for respiratory symptoms and medication use, and lung function decrements. Less consistent evidence for pulmonary inflammation.	Section 5.1.2.2 Section 0 Section 5.1.2.4	
Lack of evidence from controlled human exposure studies	In adults with asthma, most measures of lung function are unaffected. There is a lack of evidence for pulmonary inflammation.	Section 0 Section 0 Urch et al. (2010)	64 µg/m^3
Some evidence from toxicological studies at relevant concentrations	Most studies show enhancement of allergic inflammation, other allergic responses, or airway remodeling in animal model of allergic airway disease.	Section 5.1.2.4.2 Harkema et al. (2009) Wagner et al. (2012)	356–596 µg/m^3
Biological plausibility	Evidence from animal toxicological studies provides biological plausibility for epidemiologic findings for exacerbation of allergic asthma, the most common asthma phenotype in children.		

Table 5-18 (Continued): Summary of evidence for a likely to be causal relationship between short term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Exacerbation of COPD			
Consistent epidemiologic evidence from multiple, high-quality studies at relevant $PM_{2.5}$ concentrations	Increases in COPD-related hospital admissions and ED visits in studies conducted in the U.S. and Canada.	Section 5.1.4.1.1 Section 5.1.4.1.2	7.7–18.0 µg/m^3 7.1–19.2 µg/m^3
Epidemiologic evidence from a limited number of copollutant models provide some support for an independent $PM_{2.5}$ association	Limited examination of potential copollutant confounding for COPD-related hospital admissions and ED visits, with evidence that associations remain robust in models with gaseous pollutants. Limited information is available regarding models with $PM_{10-2.5}$. When reported, correlations with gaseous copollutants were primarily in the low to moderate range ($r < 0.7$).	Section 5.1.10.1	
Some coherence in epidemiologic studies across the continuum of effects	Panel studies in adults with COPD provide support for COPD exacerbation with consistent evidence of increased eNO in response to short-term $PM_{2.5}$ exposure. Less consistent evidence for respiratory symptoms and lung function.	Section 5.1.4.2 Section 5.1.4.3 Section 5.1.4.4	
Limited evidence from a controlled human exposure study and animal toxicological studies at relevant concentrations	Lung injury, inflammation and decrements in lung function are observed.	Section 5.1.4.3 Section 5.1.4.4	171–1,200 µg/m^3
Biological plausibility	Evidence from animal toxicological studies provides biological plausibility for epidemiologic findings for COPD.		
Respiratory mortality			
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Consistent evidence of increases in mortality in response to short-term $PM_{2.5}$ exposure in multicity studies in the U.S. and Canada. Evidence of immediate effects (lag 0 to 1 days), and some recent evidence of prolonged effects (lags >2 days).	Section 5.1.9	7.9–19.9 µg/m^3
Epidemiologic evidence from a limited number of copollutant models provide some support for an independent $PM_{2.5}$ association	Potential copollutant confounding is examined in a limited number of studies with some evidence that associations remain robust in models with gaseous pollutants and $PM_{10-2.5}$.	Section 5.1.10.1	

Table 5-18 (Continued): Summary of evidence for a likely to be causal relationship between short term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Some coherence with underlying causes of mortality	COPD and respiratory infection evidence provide coherence.		
Other respiratory endpoints			
Epidemiologic studies provide some evidence of an association with respiratory infection and with consistent positive associations when examining combined respiratory-related diseases	Generally positive associations in hospital admissions and ED visits for combinations of respiratory infections; with more limited and inconsistent evidence for specific respiratory infections, such as pneumonia.	Section 5.1.5.1 Section 5.1.5.2	9.8–19.2 µg/m^3 12.9–14.1 µg/m^3
	Increases in hospital admissions and ED visits for combined respiratory-related diseases in multicity studies, with expanded evidence for effects in older adults. Supporting evidence from other multicity studies as well as single city studies in children, adults, older adults, and people of all ages.	Section 5.1.6.1 Section 5.1.6.2	9.6–19.4 µg/m^3 7.1–19.2 µg/m^3
Limited evaluation of confounding by copollutants	Potential copollutant confounding remains unexamined in studies of respiratory infection	Section 5.1.10.1	
	Potential copollutant confounding is examined in a limited number studies, with evidence that associations generally remain robust in models with gaseous pollutants and $PM_{10-2.5}$.	Section 5.1.10.1	
Limited evidence from toxicological studies at relevant concentrations	Results show altered host defense and greater susceptibility to bacterial infection.	Zelikoff et al. (2003)	100–250 µg/m^3
Inconsistent epidemiologic evidence from studies of respiratory effects in healthy populations and allergy exacerbation	Short-term $PM_{2.5}$ exposures are inconsistently related to respiratory effects in panel studies of healthy adults. A limited number of panel studies in healthy children provide some evidence of an association with respiratory effects.	Section 5.1.7.1	
	Inconsistent increases in physician visits for allergic diseases and self-reported allergies across a limited number of studies.	Section 5.1.3	
Inconsistent evidence from controlled human exposure studies	Evidence is inconsistent for decrements in lung function and pulmonary inflammation.	Section 5.1.7.2	90–234 µg/m^3

Table 5-18 (Continued): Summary of evidence for a likely to be causal relationship between short term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Some evidence from toxicological studies at relevant concentrations	Results show pulmonary injury, oxidative stress, inflammation, morphologic changes, and allergic sensitization, but not in every study. Responses tend to be more robust following multiday exposures. Evidence for irritant responses (changes in respiratory rate and lung volumes) is more consistent.	Section 5.1.7.3	48–343 $\mu g/m^3$

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

Epidemiologic evidence is also expanded for COPD-related hospital admissions and ED visits. The 2009 PM ISA described consistent associations in most of those studies conducted in the U.S. or Canada. Additional U.S. analyses of the Medicare population provide supporting evidence, as do many multicity U.S. and Canadian studies. However, many studies of single cities do not indicate associations. Although recent studies add inconsistent findings, the overall evidence links recent COPD hospital admission and ED visits to short-term $PM_{2.5}$ exposures. A common uncertainty across the studies is the lack of examination of copollutants to assess the potential for confounding and compare to previous findings showing attenuation of the $PM_{2.5}$ associations with adjustment for NO_2. However, recent observations of $PM_{2.5}$-related increases in COPD symptoms, medication use, pulmonary inflammation, and decreases in lung function in epidemiologic studies support and add coherence for the hospital admission and ED visits studies. Results of controlled human exposure and animal toxicological studies show decrements in lung function, pulmonary inflammation, and lung injury, providing coherence with and biological plausibility for epidemiologic findings.

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) consistently observed associations between $PM_{2.5}$ concentrations and hospital admissions or ED visits for respiratory infections, which often encompassed multiple individual respiratory infections, but not for pneumonia alone. Recent studies expand findings but are not consistent with the results of older studies since the respiratory infection-related outcomes examined were heterogeneous. Many studies of respiratory infection did not examine any copollutants, making it unclear whether $PM_{2.5}$ associations are independent of copollutants. Results from an animal toxicological study demonstrate biological plausibility by showing altered host defense and greater susceptibility to bacterial infection as a result of short-term $PM_{2.5}$ exposure.

Studies of combined respiratory-related hospital admissions and ED visits examine groups of specific diseases or examine all respiratory-related diseases. Associations are seen in children, people of all ages, and older adults from single-city studies and in people of all ages in multicity studies. Studies of respiratory mortality also report associations in single and multicity studies, although confidence intervals are sometimes wide, as reflected by the small percentage of deaths that are due to respiratory mortality (~9%) (NHLBI, 2017). Potential copollutant confounding is examined in a few studies of aggregated respiratory condition and respiratory mortality and while there is some evidence indicating that associations remain robust in models with gaseous pollutants or $PM_{10-2.5}$, uncertainty remains.

In epidemiologic studies in healthy populations, changes in lung function and pulmonary inflammation are observed, but changes tend to be transient and copollutant confounding is inadequately examined. Controlled human exposure and animal toxicological studies provide evidence for lung function decrements and pulmonary inflammation, as well as for pulmonary injury, oxidative stress, morphologic changes, and allergic sensitization. However, effects were not observed in every study.

The strongest evidence of an effect of short-term $PM_{2.5}$ exposure on respiratory effects is provided by epidemiologic studies of asthma and COPD exacerbation. While animal toxicological studies provide biological plausibility for these findings, some uncertainty remains with respect to the independence of $PM_{2.5}$ effects. **Overall, the collective evidence is sufficient to conclude that a causal relationship is likely to exist between short-term $PM_{2.5}$ exposure and respiratory effects.**

5.2 Long-Term Exposure $PM_{2.5}$ Exposure and Respiratory Effects

The 2009 PM ISA concluded that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and respiratory effects (U.S. EPA, 2009).[57] This conclusion was based mainly on epidemiologic evidence demonstrating associations between long-term $PM_{2.5}$ exposure and changes in lung function or lung function growth rate in children. Biological plausibility was provided by a single animal toxicological study involving pre- and post-natal exposure to $PM_{2.5}$ CAPs which found impaired lung development. Epidemiologic evidence for associations between long-term $PM_{2.5}$ exposure and other respiratory outcomes such as the development of asthma, the development of allergic disease, the development of COPD, respiratory infection, and the severity of disease was limited, both in the number of studies available and the consistency of the results. In an animal toxicological study, long-term exposure to $PM_{2.5}$ CAPs also led to morphological changes in nasal airways of healthy animals. Additional animal toxicological studies involved exposure to mixtures, such as motor vehicle exhaust and woodsmoke, and effects were not attributed to the particulate or gaseous components of the mixture.

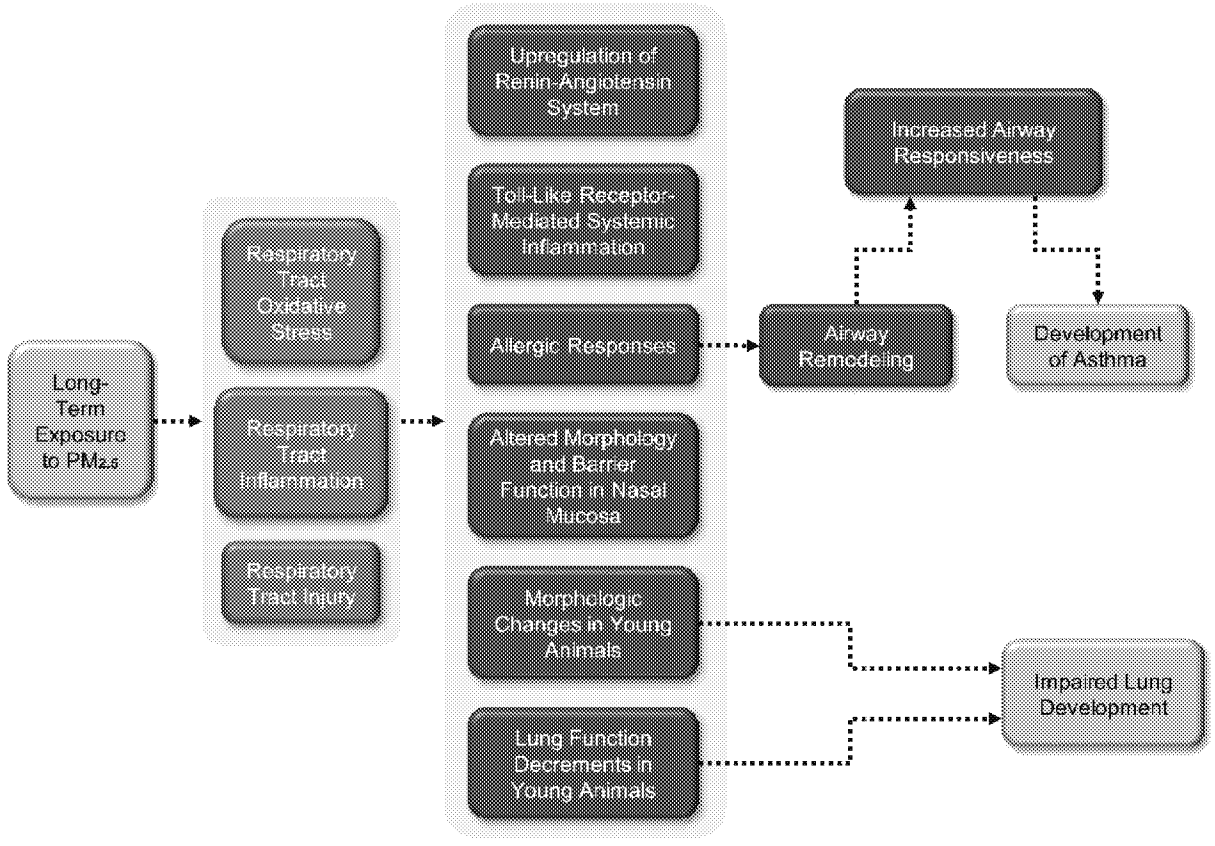
[57] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations unless otherwise noted.

Recent evidence continues to link long-term exposure to $PM_{2.5}$ and reduced lung development in children and supports $PM_{2.5}$-related acceleration of lung function decline in adults (Section 5.2.2). The recent body of literature enhances the limited evidence base, providing further evidence that long-term exposure to $PM_{2.5}$ is associated with asthma development in children (Section 5.2.3) and COPD development in adults (Section 5.2.5). Epidemiologic evidence for the development of allergic disease (Section 5.2.4), respiratory infection (Section 5.2.6), and severity of disease (Section 5.2.7) is inconsistent. Recent animal toxicological studies provide evidence for respiratory effects in healthy populations (Section 5.2.8) and animal models of cardiovascular disease (Section 5.2.9), including pulmonary oxidative stress and inflammation. Studies focusing on the nasal airways find inflammation and morphologic changes (Section 5.2.8). The epidemiologic literature provides evidence for respiratory mortality in relationship to long-term $PM_{2.5}$ exposure (Section 5.2.10) and examines the relationship between the decline in $PM_{2.5}$ levels and metrics of respiratory health (Section 5.2.11). Findings that improved respiratory health in children are linked to decreased $PM_{2.5}$ concentrations add to the evidence base linking long-term $PM_{2.5}$ exposure and respiratory effects. However, uncertainty with respect to copollutant confounding remains.

5.2.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory health effects resulting from long-term exposure to $PM_{2.5}$. Figure 5-27 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that lead to downstream events observed in epidemiologic studies. This discussion of "how" long-term exposure to $PM_{2.5}$ may lead to respiratory health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 0.

Once $PM_{2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). Insoluble and soluble components of $PM_{2.5}$ may interact with respiratory tract cells, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential." Furthermore, respiratory tract cells may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, insoluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, whereas the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-27 Potential biological pathways for respiratory effects following long-term $PM_{2.5}$ exposure.

Evidence that long-term exposure to $PM_{2.5}$ may affect the respiratory tract generally informs one proposed pathway (Figure 5-27). It begins with injury, oxidative stress, and inflammation in the respiratory tract, as demonstrated by animal toxicological studies. These responses, which are difficult to disentangle, were also observed in some studies of short-term exposure to $PM_{2.5}$ (Figure 5-1). Persistent or intermittent exposure to $PM_{2.5}$ over months to years may lead to cumulative or chronic effects, including the development of asthma or impaired lung development, as measured by decrements in lung function growth.

Inhalation of CAPs resulted in the upregulation of the renin-angiotensin system (RAS), as indicated by an increase in mRNA and protein levels of angiotensin receptor Type 1, in rodent lung tissue

(Aztatzi-Aguilar et al., 2015). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. This response was accompanied by upregulation of heme oxygenase-1, an antioxidant enzyme induced in response to oxidative stress. Whether upregulation of the RAS was mediated by inflammation or oxidative stress is not clear. The SNS and the RAS are known to interact in a positive feedback fashion (Section 8.1.2) with important ramifications in the cardiovascular system. But, there is no evidence that long-term exposure to $PM_{2.5}$ leads to activation of sensory nerves or to modulation of ANS responses, as was observed in the case of short-term exposure to $PM_{2.5}$ (Figure 5-1). Thus, there is no evidence to support a relationship between activation of sensory nerves and changes in the RAS following long-term exposure to $PM_{2.5}$.

Some animal toxicological studies shed light on specific types of inflammation such as Th1 and Th2 innate immunity. Long-term inhalation of CAPs increased levels of oxidized phospholipids in the BALF (Deiuliis et al., 2012; Kampfrath et al., 2011). Specific macrophage and T-cell subtypes were also increased in lung tissue. These results are consistent with the known role of oxidized phospholipids in activating the Toll-like Receptor (TLR4) system. The TLR4 system stimulates macrophages to release cytokines that recruit and activate T cells. This response is a proinflammatory Th1 innate immune response capable of transmitting cell signals to the systemic circulation, leading to systemic inflammation (see Section 6.2.1). Th2 innate immune responses were also demonstrated following inhalation of $PM_{2.5}$. Long-term exposure to diesel exhaust particles (DEPs) resulted in increased levels of Th2 cytokines in BALF (Kim et al., 2016a). This response was accompanied by methacholine-induced changes in enhanced pause (Penh), which may indicate an increase in airway responsiveness. These changes are consistent with the development of an allergic asthmatic phenotype and possibly underlie epidemiologic findings linking exposure to $PM_{2.5}$ and the development of asthma (Section 5.2.3).

Other animal toxicological studies focused on respiratory responses in a specific region (e.g., the nose) or in the context of a specific disease state (e.g., cardiovascular disease) or lifestage (e.g., young animals). Oxidative stress, injury, inflammation, and morphologic changes were demonstrated in nasal mucosa following long-term exposure to $PM_{2.5}$ (Guo et al., 2017);(Guo et al., 2017; Ramanathan et al., 2017). Findings of increased malondialdehyde, cytokines, numbers of eosinophils and neutrophils, markers of eosinophil and neutrophil activation, as well as nasal epithelial necrosis, increased septal thickness, and sinonasal epithelial cell barrier dysfunction were reported. Inflammatory responses, such as upregulation of cytokine mRNA and monocytic infiltration in the lung, were found in two animal models of cardiovascular disease following CAPs exposure (Ying et al., 2015; Xu et al., 2012). Experimental studies in young animals exposed to $PM_{2.5}$ also demonstrated oxidative stress-related changes in lungs following pre- and post-natal exposures (Song et al., 2017) and secretory changes in nasal mucosa following neonatal exposure (Pires-Neto et al., 2006). Further, inhalation of CAPs in the pre- and post-natal period resulted in decreased lung function (i.e., decreased inspiratory and expiratory volumes) and altered lung morphology (i.e., decreased alveolar surface to volume ratio) (Mauad et al., 2008). These changes reflect impaired lung development likely due to incomplete alveolarization and the enlargement

of air spaces as a result of exposure to $PM_{2.5}$. They provide plausibility for decrements in lung function growth seen in epidemiologic studies (Section 5.2.2).

As described here, there is one main pathway, with many branches, by which long-term exposure to $PM_{2.5}$ could lead to respiratory health effects. It involves respiratory tract injury, inflammation, and oxidative stress as initial events. There is evidence of Th1 and Th2 innate immune system activation. The latter response, indicating the development of an allergic phenotype, may lead to increases in airway responsiveness, which are linked to the development of asthma. Inflammatory changes in the upper respiratory tract (i.e., the nose) of adult animals likely triggered the observed morphologic changes and barrier dysfunction. Respiratory tract inflammation may also lead to morphologic changes and lung function decrements in young animals, which are linked to impaired lung development. The multibranched pathway described here provides biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.2.13).

In addition, evidence for Type 1 innate immune system activation in the respiratory tract provides a link to systemic inflammation resulting from long-term exposure to $PM_{2.5}$ (Section 6.2.1). This pathway may contribute to extrapulmonary effects following inhalation of $PM_{2.5}$.

5.2.2 Lung Function and Development

In the 2009 PM ISA (U.S. EPA, 2009), the strongest evidence for a relationship between long-term $PM_{2.5}$ exposure and respiratory effects was provided by epidemiologic studies examining lung function or lung function growth rate in children. Changes in lung function over time in children are indicative of lung development. In adults, lung function measurements may provide an indicator of declining lung function over time. Epidemiologic evidence supported an association between long-term $PM_{2.5}$ exposure and reduced lung development in children in different cohorts and locations. An animal toxicological study provided support for the epidemiologic evidence since pre- and post-natal exposure to ambient levels of urban particles was found to impair mouse lung development. Recent studies provide further support demonstrating a relationship between long-term exposure to $PM_{2.5}$ and reduced lung development in children as well as the possible acceleration of lung function decline in adults.

5.2.2.1 Lung Development

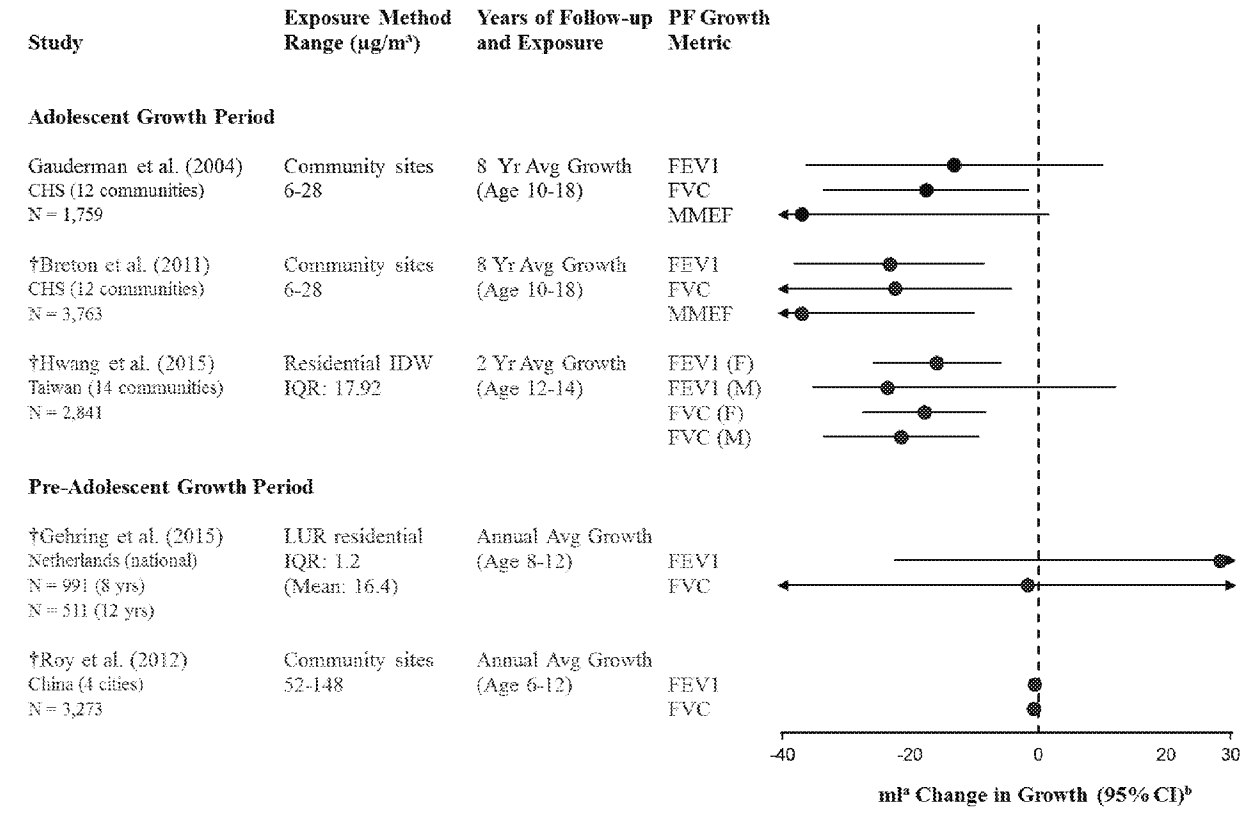
Lung development occurs from the fetal period through early adulthood, comprising a long window of potential vulnerability to environmental stressors, such as PM (Stanojevic et al., 2008; Zeman and Bennett, 2006; Thurlbeck, 1982). Lung function measures capture the cumulative effects of pulmonary growth, damage, and repair (Wang et al., 1993). As such, measures of lung function are

effective indicators of pulmonary health, and changes in lung function over time are indicative of lung development.

5.2.2.1.1 Epidemiologic Studies

Epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) indicated that long-term exposure to $PM_{2.5}$ is associated with decrements in lung development in schoolchildren. Key evidence informing the relationship came from analyses of the Children's Health Study (CHS), a prospective cohort study of children in 12 southern California communities. Two studies of this cohort that were reviewed in the 2004 PM AQCD (U.S. EPA, 2009) observed decrements in annual pulmonary growth rates for all of the examined lung function measures (FVC, FEV_1, MMEF, and FEF_{75}) in relation to long-term in $PM_{2.5}$ exposure (Gauderman et al., 2002; Gauderman et al., 2000). Gauderman et al. (2000) examined lung function growth over a 4-year period for three age cohorts within CHS, including 4th graders, 7th graders, and 10th graders. The authors consistently reported the strongest associations, in magnitude and precision, in 4th graders and the weakest associations in 10th graders for all lung development metrics. A study reviewed in the 2009 PM ISA expanded on the previous CHS analyses, following children for 8 years (Gauderman et al., 2004). Gauderman et al. (2004) reported that PM-related deficits in average lung development between ages 10 and 18 years resulted in clinically important deficits in attained lung function at age 18 (Gauderman et al., 2004).

Recent data from studies based in the U.S. and Asia continue to provide evidence for $PM_{2.5}$-related decrements in lung development in children (Figure 5-28). The focus of this section is on longitudinal epidemiologic studies conducted in cohorts in diverse locations with a wide range of ambient $PM_{2.5}$ concentrations. Study-specific details, air quality characteristics, and select results from these studies are highlighted in Table 5-19. The CHS is further evaluated in recent studies that provide supporting evidence in multiple cohorts recruited in 1993 and 1996 and followed through 2007 (Gauderman et al., 2015; Breton et al., 2011). Recent results from the CHS not only corroborate previous results, but they also indicate improvements in lung development in association with declining $PM_{2.5}$ concentrations (Gauderman et al., 2015) (Section 5.2.11). Results from the CHS indicate that long-term $PM_{2.5}$ exposure may impact lung development during adolescence (age 10−18 years), a period of rapid, nonlinear growth (Wang et al., 1993). Associations during adolescence also are supported in a multicity cohort in Taiwan (Hwang et al., 2015). However, mean $PM_{2.5}$ concentrations in this study were notably higher than those in the CHS studies. As examined in a limited number of recent studies, evidence is less clear for effects during the linear growth period of preadolescence. $PM_{2.5}$ was associated with reduced lung development in a cohort in China that included children ages 6−12 years at baseline (Roy et al., 2012). However, no association was observed between $PM_{2.5}$ and lung development in the PIAMA cohort between ages 8 and 12 years (Gehring et al., 2015a). Information on critical periods of exposure is limited, as most studies examined concurrent exposure. In the PIAMA cohort, lung development was not associated with $PM_{2.5}$ exposure estimated for the concurrent period or birth year (Gehring et al., 2015a).



CHS = Children's Health Study, CI = confidence interval, F = female, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IDW = inverse distance weighting, IQR = interquartile range, LUR = land use regression, M = male, MMEF = maximum midexpiratory flow.

[a]FEV_1 and FVC are measured in ml, MMEF is measured in ml/s.

[b]Effect estimates are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$.

Note: †Studies published since the 2009 PM ISA. Black text/circles = studies evaluated in the 2009 PM ISA. Red text/circles = studies published since the completion of the 2009 PM ISA. Corresponding quantitative results and study details are reported in Table 5-19.

Figure 5-28 Longitudinal repeated measure studies of $PM_{2.5}$ and lung development.

Table 5-19 Associations of $PM_{2.5}$ with lung development in children from longitudinal studies with repeated measures.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
Gauderman et al. (2004) 12 southern California communities 1993–2000	CHS 1993 cohort n = 1,759 Followed ages 10–18 yr 10% loss to follow up per yr	One monitor in each of 12 communities Children's homes and schools in same neighborhoods as monitoring sites (Navidi et al., 1999; Navidi et al., 1994). Annual avg, concurrent exposure Range of means across communities: 6–28 μg/m^3	Change in 8-yr average growth: FVC (ml): −13.2 (−36.4, 10.1) FEV_1 (ml): −17.5 (−33.6, −1.4) MMEF (ml/s): −37.0 (-75.8, 1.7)	Correlation (*r*): 0.33 O_3, 0.79 NO_2, 0.87 Acid Vapor Copollutant models with: NA
†Breton et al. (2011) 12 southern California communities 1993 or 1996–2000	CHS 1993 and 1996 cohorts N = 2,106 Followed ages 10–18 yr 10% loss to follow up per yr (No evidence of relation between participation and baseline lung function or air pollution exposure)	One monitor in each of 12 communities Children's homes and schools in same neighborhoods as monitoring sites (Navidi et al., 1999; Navidi et al., 1994). Annual avg, concurrent exposure Range of means across communities: 6–28 μg/m^3	Change in 8-yr average growth: FVC (ml): −23.3 (−38.3, −8.4) FEV_1 (ml): −22.5 (−40.7, −4.2) MMEF (ml/s): −37.0 (−64.1, −10.0)	Correlation (*r*): 0.79 NO_2 Copollutant models with: NA

Table 5-19 (Continued): Associations of $PM_{2.5}$ with lung development in children from longitudinal studies with repeated measures.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
†Gauderman et al. (2015) Five southern California communities 1994–2011	CHS 1994–1998, 1997–2001, and 2007–2011 cohorts N = 2,120 Followed ages 11–15 yr 25% loss to follow up. (No evidence of relation between participation and baseline lung function or air pollution exposure)	One monitor in each of five communities. 4-yr avg Range of means across communities: 21.3–31.5 μg/m^3 in 1994–1997 and 11.9–17.8 μg/m^3 in 2007–2010	Change in 4-yr average growth per decrease in $PM_{2.5}$[b]: FEV_1 (ml): 26.0 (6.8, 45.2) FVC (ml): 50.4 (26.1, 74.6)	Correlation (*r*): 0.82 NO_2, 0.39 O_3 Copollutant models with: NA
†Gehring et al. (2015a) The Netherlands 1996–2010	PIAMA N = 3,702 Followed age 8–12 yr 15% original cohort had data at age 8 and 12 yr	Annual avg estimated at birth residence (birth year) and current address (at time of questionnaire) using LUR. LOOCV R^2 = 0.61. Mean: 16.4 μg/m^3 75th: 25.3 μg/m^3 95th: 26.4 μg/m^3	Change in annual average growth: FVC (ml): −1.7 (−41.3, 37.9) FEV_1 (ml): 28.3 (−22.5, 79.2)	Correlation (*r*): 0.73 NO_2 (at birth address) Copollutant models with: NA
†Hwang et al. (2015) 14 Taiwan communities	TCHS N = 2,941 Followed age 12–14 yr 8.6% loss to follow up	14 monitors combined by IDW to obtain ambient $PM_{2.5}$ concentration estimates outside each home. Annual avg, concurrent exposure Mean: 34.5 μg/m^3 75th: 43.8 μg/m^3	Change in 2-yr average growth: Boys FEV_1 (ml): −23.7 (−35.3, 12.2) FVC (ml): −21.5 (−33.7, −9.2) Girls FEV_1 (ml): −15.9 (−26.0, −5.7) FVC (ml): −17.8 (−27.5, −8.2)	Correlation (*r*): NO_2: 0.25 NO_2, 0.0$_3$ CO, 0.69 SO_2 Copollutant models with: NO_2 and CO

Table 5-19 (Continued): Associations of $PM_{2.5}$ with lung development in children from longitudinal studies with repeated measures.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
†Roy et al. (2012) Four China cities	N = 3,273 Followed 3 yr from age 6–12 yr 24% with ≥3 measures. Sensitivity analyses show results not biased due to loss to follow-up	School outdoor monitors 3-yr avg and 3-mo avg concurrent exposure Mean: 148 µg/m^3 urban Guangzhou 52 µg/m^3 suburban Wuhan	Change in annual average growth: FEV_1 (ml): −0.7 (−0.9, −0.5) FVC (ml): −0.7 (−1.0, −0.5)	Correlation (*r*): NA Copollutant models with: NA

CHS = Children's Health Study, CI = confidence interval, CO = carbon monoxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IDW = inverse distance weighting, IQR = interquartile range, LOOCV = leave one out cross-validation, LUR = land use regression, M = male, MMEF = maximum midexpiratory flow, NO_2 = nitrogen dioxide, NR = not reported, PIAMA = Prevention and Incidence of Asthma and Mite Allergy, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, SD = standard deviation, SO_2 = sulfur dioxide, TCHS = Taiwan Children's Health Study.

[a]Effect estimates are standardized to a 5 µg/m^3 increase in $PM_{2.5}$.

[b]Effect estimates are standardized to a 5 µg/m^3 decrease in $PM_{2.5}$.

†Studies published since the 2009 PM ISA.

1

Copollutant Confounding and Other Sources of Uncertainty

Due to a limited number of studies that examined potential copollutant confounding, uncertainty remains in distinguishing an independent effect of long-term $PM_{2.5}$ exposure on lung development. In the only study to report results from copollutant models, Hwang et al. (2015) observed that $PM_{2.5}$-associated decrements in lung development persisted in copollutant models that included NO_2 or CO. NO_2 and CO were weakly correlated with $PM_{2.5}$ ($r = 0.25$ and 0.03, respectively). Other studies that reported copollutant correlations observed moderate to high correlations for most pollutants (NO_2: $r = 0.73–0.87$, SO_2: $r = 0.69$, O_3: $r = 0.33–0.39$; Table 5-19).

Because results for lung development are based on changes in lung function measured over time, loss to follow up and the method of lung function assessment could be additional sources of error or bias. However, neither is indicated to have systematically influenced the evidence for $PM_{2.5}$ associations. As detailed in Table 5-19, attrition of 10% or less was reported in some studies (Hwang et al., 2015; Breton et al., 2011). Others reported higher loss to follow-up (Gauderman et al., 2015; Gehring et al., 2015a; Roy et al., 2012), but reported similar characteristics between participants and nonparticipants, or no relation between participation and either baseline lung function or exposure to air pollution. Additionally, in a study that had changes in the device used to measure lung function, $PM_{2.5}$ associations were robust to adjustment for a factor representing the difference between devices (Gauderman et al., 2015).

Finally, the CHS studies in this section rely on exposure estimates from single fixed-site monitors within each community, which may result in misclassification of exposure. However, analyses of some individual CHS communities show low-to-moderate spatial heterogeneity of ambient $PM_{2.5}$ concentrations. In Long Beach, CA, $PM_{2.5}$ concentrations were moderately to highly correlated ($r = 0.67–0.91$) across four sites within 6.4 km of each other, including two schools attended by CHS cohort subjects (Krudysz et al., 2008). In Riverside, CA, $PM_{2.5}$ concentrations at a fixed-site monitor explained 96% of the variance in concentrations outside the homes of children with asthma (Ducret-Stich et al., 2012). Further, an analysis of multiple CHS communities described monitoring sites in some but not all communities as well representing the range of residential and school outdoor $PM_{2.5}$ concentrations of subjects. Thus, long-term concentrations measured at fixed-site monitors are unlikely to introduce major exposure measurement error.

5.2.2.1.2 Animal Toxicological Studies

The 2009 PM ISA evaluated studies that examined lung development. These studies involved early life exposure to ambient levels of urban particles in Sao Paulo, Brazil (Mauad et al., 2008; Pires-Neto et al., 2006). Urban air PM mainly consisted of $PM_{2.5}$, but it also contained some PM_{10}; other ambient pollutants were also present. Control mice were exposed to filtered urban air, which contained greatly reduced concentrations of PM. Mauad et al. (2008) found decreased inspiratory and expiratory

volumes in mice exposed both pre- and postnatally compared to control animals. Alveolar surface to volume ratio was also decreased in animals exposed during both the pre- and post-natal periods. No changes in lung function or morphology were observed in animals exposed only prenatally or only postnatally. These results reflect altered lung development resulting from $PM_{2.5}$ exposure. Pires-Neto et al. (2006) found secretory changes in the nasal cavity of neonatal mice exposed for 5 months to urban PM from Sao Paulo Brazil. Specifically, production of acidic mucosubstances was increased, potentially representing impaired respiratory defense mechanisms. Interpretation of effects due to long-term urban air exposure is complicated by the presence of $PM_{10-2.5}$. Recently, Song et al. (2017) demonstrated changes in lung molecular clock gene expression resulting from pre- and post-natal exposure of rats to ambient levels of urban particles in Beijing, China. Control rats were exposed to filtered urban air, which contained greatly reduced concentrations of PM. In addition, altered lung morphology and oxidative stress were observed in rat pups and in pregnant rats. These findings are discussed in Section 9.3.3.

5.2.2.2 Lung Function

The relationship between long-term $PM_{2.5}$ exposure and lung function in children and in adults was examined in numerous epidemiologic studies.

5.2.2.2.1 Children

In addition to lung development, a number of studies examine the effects of long-term $PM_{2.5}$ exposure in relation to attained pulmonary function at a given point in time. Epidemiologic studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) indicated that long-term exposure to $PM_{2.5}$ is associated with decrements in attained lung function in children. Notably, in the CHS analysis described in Section 5.2.2.1.1, Gauderman et al. (2004) observed that 18-year-olds had increased risk of clinically low FEV_1 measurements at age 18 in communities with higher $PM_{2.5}$ concentrations. However, unlike the results reported for lung development, the attained lung function estimates did not include adjustment for potential confounders, introducing uncertainty into the interpretation of the results. European birth cohort studies also generally reported evidence of an effect on lung function metrics when examining long-term $PM_{2.5}$ exposure (Oftedal et al., 2008; Schikowski et al., 2005; Ackermann-Liebrich et al., 1997), but results were not entirely consistent (Gotschi et al., 2008). None of the lung function studies reviewed in the 2009 PM ISA examined copollutant models. Recent studies available for review add to the existing evidence supporting an association between long-term exposure to $PM_{2.5}$ and decreased lung function in children. These studies examine a variety of exposure periods, exposure methods, cohorts, locations, and exposure levels. Additionally, a limited number of copollutant models indicate that the observed $PM_{2.5}$ effect may be independent of NO_2, CO, and O_3 exposures. Study-specific details, air quality characteristics, and select results from these studies are presented in Table 5-20.

Table 5-20 Associations of $PM_{2.5}$ with lung function in children and adults.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
Children				
†Gehring et al. (2013) Germany, Sweden, the U.K., and the Netherlands	ESCAPE Project: BAMSE, GINIplus, LISAplus, MAAS, and PIAMA n = 5,357 Followed to ages 6–8	Annual avg $PM_{2.5}$ concentrations estimated at birth residence (birth year) and current address (at time of lung function measurement) using LUR. LOOCV R^2 = 0.21–0.78 RMSE: 0.8–1.2 Mean: 7.8–17.4 µg/m^3	Current address exposure FEV_1 (percent diff.): −2.5 (−4.6, −0.4) FVC (percent diff.): −8.8 (−20.5, 4.5) PEF (percent diff.): −2.1 (−4.1, −0.1) FEV_1 <85% predicted (OR): 1.41 (0.74, 2.71)	Correlation (*r*): 0.75 NO_2, 0.57 NO_X, 0.50 PM_{10}, 0.58 $PM_{10-2.5}$ Copollutant models with: NO_2
†Wang et al. (2015b) The Netherlands 1996–2005	PIAMA n = 1,058 Followed to age 8 68% participation rate	Annual avg $PM_{2.5}$ concentrations estimated at current address (at time of lung function measurement) using LUR. LOOCV R^2 = 0.61 RMSE: 1.21 Median: 16.5 µg/m^3 IQR: 15.6–16.7 µg/m^3 Alternatively, dispersion models predicted $PM_{2.5}$ concentration at a 1-km × 1-km grid level. Median: 16.8 µg/m^3 IQR: 13.6–17.3 µg/m^3	Results presented graphically. LUR and dispersion model $PM_{2.5}$ estimates were associated with decreased FEV_1 and FVC, but not PEF. Associations were stronger but less precise using LUR $PM_{2.5}$ estimates.	Correlation (*r*): 0.75 NO_2 (LUR), 0.92 NO_2 (Dis.) Copollutant models with: NO_2

Table 5-20 (Continued): Associations of $PM_{2.5}$ with lung function in children and adults.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
†Rice et al. (2015b) Massachusetts 1999–2010	Project Viva—pre-birth cohort n = 614 Followed to a mean age of 7.7 yr	Annual avg $PM_{2.5}$ concentrations for first year of life, previous year, and lifetime exposure were estimated at 10 × 10 km grid level using AOD observation data from satellite imagery. Resolved to 50 × 50 m using land use terms and assigned to participants' home addresses. 10-fold cross-validated LOOCV R^2: 0.83 First year mean: 12.1 µg/m^3 Lifetime mean: 10.7 µg/m^3 Last year mean: 9.4 µg/m^3	Last year exposure FEV_1 (ml): −60.3 (−112, −8.5) FVC (ml): −54.5 (−110, 0.5) FEV_1 <80% predicted (OR): 2.4 (1.1, 5.2) FVC <80% predicted (OR): 1.7 (0.4, 6.7)	Correlation (*r*): NA Copollutant models with: NA
†Urman et al. (2014) Southern California 2002–2008	CHS n = 1,811 Followed to ages 5–7 82% participation	One monitor in each of 12 communities Children's homes and schools in same neighborhoods as monitoring sites (Navidi et al., 1999; Navidi et al., 1994). 6-yr avg, (lifetime) exposure Range of means across communities: 6–28 µg/m^3	FEV_1 (percent diff.): −1.1 (−1.7, −0.5) FVC (percent diff.): −0.8 (−1.5, −0.2)	Correlation (*r*): 0.8 PM_{10}, 0.6 NO_2 Copollutant models with: NA
†Eenhuizen et al. (2013) The Netherlands 1996–2001	PIAMA n = 880 Followed to age 4 49% of participants had valid Rint data	Annual avg $PM_{2.5}$ concentrations estimated at current address (at time of lung function measurement) using LUR. LUR model explained 73% of $PM_{2.5}$ spatial variability. Median: 16.9 µg/m^3 IQR: 14.9–18.2 µg/m^3	Change in Rint (kPA•S•L^{-1}) 0.06 (0.02, 0.11)	Correlation (*r*): 0.93 NO_2 Copollutant models with: NA
†Gehring et al. (2015a) The Netherlands 1996–2010	PIAMA n = 3,702 Followed age 8–12 yr 15% original cohort had data at age 8 and 12 yr	Annual avg $PM_{2.5}$ concentrations estimated at current address (at time of lung function measurement) using LUR. LOOCV R^2 = 0.61. Mean: 16.4 µg/m^3 75th: 25.3 µg/m^3 95th: 26.4 µg/m^3	Current address exposure FEV_1 (percent diff.): −4.2 (−9.2, 0.8) FVC (percent diff.): −2.9 (−7.5, 1.7) FEF_{25-75} (percent diff.): −10.0 (−25.4, 6.3)	Correlation (*r*):0.73 NO_2 (at birth address) Copollutant models with: NA

Table 5-20 (Continued): Associations of $PM_{2.5}$ with lung function in children and adults.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
Adults				
Rice et al. (2015a) Northeastern U.S. 1995–2011	Framingham Heart Study n = 4,872 Participants had at least two spirometry measurements between 1995 and 2011. Mean age was 50.4 yr (SD: 12.4)	Annual average $PM_{2.5}$ concentrations were estimated in the index year (2001) using satellite imagery to create a 10 × 10 km spatial grid across the Northeast. Estimates were resolved to residences within a 50 × 50 m grid using land use terms. 10-fold CV R^2 = 0.85 Mean: 10.8 µg/m^3 Max: 21.7 µg/m^3	Difference in annual rate of change: FEV_1 (ml/yr): −5.25 (−10.25, −0.5) FVC (ml/yr): −5.0 (−10.25, 0.25) FEV_1/FVC (percent/yr): −0.03 (−0.10, 0.05) Difference in mean lung function: FEV_1 (ml): −33.8 (−66.5, −0.8) FVC (ml): −46.8 (−84.0, −9.5) FEV_1/FVC (%): 0.0 (−0.5, 0.5)	Correlation (*r*): NA Copollutant models with: NA
Adam et al. (2015) Cohorts across Europe 1985–2009	ESCAPE project study of five European Cohorts: ECRHS, EGEA, NSHD, SALIA, and SAPALDIA. n = 7,613 Participants had two spirometry measurements. The baseline measurement was between 1985 and 1995, depending on the cohort. The follow-up measurement was between 2001 and 2010. Mean age ranged from 43.0 to 73.3 yr across cohorts.	Annual average $PM_{2.5}$ concentrations estimated using land-use regression to spatially refine estimates from city-level monitors between 2008 and 2011. Mean: 9.5–17.8 across cohorts. IQR: 1.1–7.0 across cohorts.	Difference in annual rate of change: FEV_1 (ml/yr): −0.14 (−2.26, 1.98) FVC (ml/yr): −1.37 (−4.04, 1.29) Difference in mean lung function: FEV_1 (ml): −21.14 (−56.37, 14.08) FVC (ml): −36.39 (−83.29, 10.50)	Correlation (*r*): NA Copollutant models with: NA

Table 5-20 (Continued): Associations of $PM_{2.5}$ with lung function in children and adults.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
Adar et al. (2015) Six U.S. states 2004–2007	MESA n = 3,791 Randomly selected MESA participants completed spirometry measurements. 45–84 yr old	Time varying annual avg ambient $PM_{2.5}$ concentration based on residential history (spatio-temporal model). 1-yr avg the year prior to baseline exam. 20-yr avg for models derived from AQS estimates of PM_{10} and $PM_{2.5}/PM_{10}$ ratio. Model fit R^2 = 0.90–0.97; CV R^2 = 0.72 1-year mean: 14.2 µg/m^3 20-year mean: 22.2 µg/m^3	Difference in mean lung function: 1-yr avg FEV_1 (ml): −20 (−80, 41) FVC (ml): −59 (−132, 13) FEV_1/FVC (%): 0.2 (−0.9, 1.3) 20-yr avg FEV_1 (ml): −13 (−37, 11) FVC (ml): −6 (−35, 22) FEV_1/FVC (%): −0.3 (−0.7, 0.2)	Correlation (*r*): 0.5–0.6 NO_X, 0.7–0.9 PM_{10} Copollutant models with: NA
Boogaard et al. (2013) The Netherlands (multicity) 2008–2010	12 locations in the Netherlands N = 640 Participants had two respiratory function exams 2 yr apart (pre- and post-traffic policy-related air pollution reduction). 83% ≥30 yr old 89% ≥18 yr old	Average $PM_{2.5}$ concentrations were estimated from monitors at 12 locations that took six 1-week samples over a 6 mo period. Mean: 16.0 µg/m^3 Max: 19.4 µg/m^3	Percent change in FVC per decrease in $PM_{2.5}$[b]: 1.67 (−0.40, 3.75)	Correlation (*r*): NA Copollutant models with: NA

CHS = Children's Health Study, CI = confidence interval, CO = carbon monoxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IDW = inverse distance weighting, IQR = interquartile range, LOOCV = leave one out cross-validation, LUR = land use regression, M = male, MESA = Multi-Ethnic Study of Atherosclerosis, MMEF = maximum midexpiratory flow, NO_2 = nitrogen dioxide, NR = not reported, PIAMA = Prevention and Incidence of Asthma and Mite Allergy, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, Rint = interrupter resistance, SD = standard deviation, SO_2 = sulfur dioxide, TCHS = Taiwan Children's Health Study.

[a]Effect estimates are standardized to a 5 µg/m^3 increase in $PM_{2.5}$.

[b]Effect estimates are standardized to a 5 µg/m^3 decrease in $PM_{2.5}$.

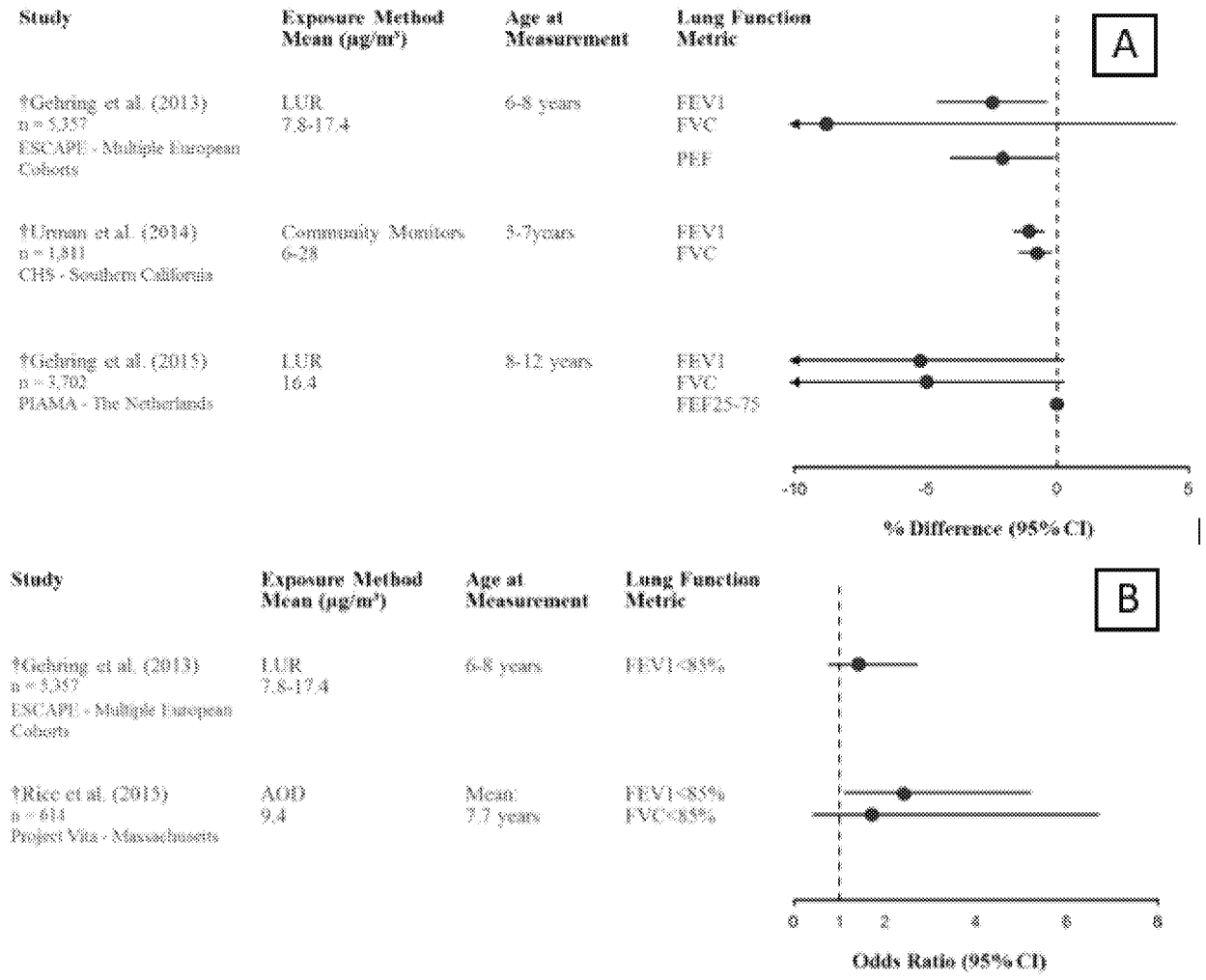
†Studies published since the 2009 PM ISA.

Recently reviewed studies provide consistent evidence that long-term exposure to $PM_{2.5}$ is associated with decreased lung function in children (Figure 5-29 and Table 5-20). Like the results from Gauderman et al. (2004), a small prebirth cohort study in Massachusetts (Rice et al., 2015b) and an ESCAPE analysis of multiple European cohorts Gehring et al. (2013) observed increased odds of clinically low FEV_1 and FVC measurements in relation to long-term $PM_{2.5}$ exposure. Associations between $PM_{2.5}$ and lung function were also observed as a measure of percent difference or absolute change in spirometry measures in the aforementioned studies (Rice et al., 2015b; Gehring et al., 2013), the CHS cohort (Urman et al., 2014), and the PIAMA cohort (Gehring et al., 2015a; Wang et al., 2015b).

The reviewed studies used an array of exposure assessment methods to produce long-term $PM_{2.5}$ estimates, including LUR models, dispersion models, hybrid models incorporating AOD observation data with land use variables, and fixed-site monitors. Associations were evident across the various exposure assignment techniques. Wang et al. (2015b) directly compared results from dispersion- and land-use regression (LUR)-modeled $PM_{2.5}$ estimates in relation to lung function metrics. The authors observed $PM_{2.5}$-related decreases in FEV_1 and FVC for both exposure assessment techniques, but noted larger but less precise (i.e., wider 95% CIs) decreases for LUR-modeled increases in $PM_{2.5}$ (quantitative results not provided; results presented graphically). These results suggest robust evidence of an association despite differences in exposure measurement error across exposure assessment methods.

Most of the reviewed studies focused on lung function in 6 to 8-year-old children. Obtaining valid spirometric lung function data is sometimes not possible in younger children. Alternatively, interrupter resistance (Rint) is a reliable technique to assess airway resistance in preschool aged children. In the PIAMA cohort, Eenhuizen et al. (2013) reported increases in Rint consistent with long-term $PM_{2.5}$ exposure estimated outside participants' birth addresses. Higher Rint was associated with lower FEV_1 levels at age 8, suggesting that Rint may be a predictor of later lung function.

A few studies examined varying windows of exposure to assess periods of potential sensitivity to PM exposure. Rice et al. (2015b) incorporated satellite-derived aerosol optical depth (AOD) observations into a land use regression model to estimate participants' exposure to ambient $PM_{2.5}$ in the first year of life, in the year prior to lung function testing, and averaged over their lifetime. The observed associations across lung function metrics were consistently stronger in magnitude, but not always precision, for $PM_{2.5}$ concentrations estimated in the year prior to examination. A similar finding was reported in the European study of cohorts for air pollution effects (ESCAPE) project analysis. Gehring et al. (2013) noted higher effect estimates for FEV_1 in relation to a 5 $\mu g/m^3$ increase in outdoor $PM_{2.5}$ concentrations estimated at current residence at the time of lung function measurement (−2.49% difference [95% CI: −4.57, −0.36]) compared to exposure assigned at the participants' birth address (−1.22% [95% CI: −3.30, 0.80]). Notably, the ESCAPE project and the prevention and incidence of asthma and mite allergy (PIAMA) cohort, discussed with regards to exposure windows in Section 5.2.3.1, use LUR models to estimate exposure after follow-up. The LUR was constructed for the cohort's current age and adjusted based on the year of lung function testing. The ratio of $PM_{2.5}$ concentration at a fixed-site monitor in the year of birth and during the year of lung function testing was used to extrapolate concentrations back to birth year at the birth residential location for each participant. Hence, changes in spatial variability between birth and the year of lung function testing were not captured. Despite the resulting uncertainty, the potentially enhanced lung-function sensitivity to $PM_{2.5}$ exposures closer to lung function examination may explain why the CHS analysis by Urman et al. (2014), which implemented a surrogate for lifetime-exposure, observed a smaller effect estimate than studies that used current address or previous year $PM_{2.5}$ estimates (Table 5-20).



AOD = aerosol optical depth, CHS = Children's Health Study, CI = confidence interval, FEF_{25-75} = forced expiratory flow at 25–75% of the pulmonary volume, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, LUR = land use regression.

Note: †Studies published since the 2009 PM ISA. Panel A depicts percent difference in lung function metrics. Panel B depicts odds of lung function metrics below normal levels (85% predicted). Red text/circles = studies published since the completion of the 2009 PM ISA. Effect estimates are standardized to a 5 µg/m^3 increase in $PM_{2.5}$. Corresponding quantitative results and study details are reported in Table 5-20.

Figure 5-29 Long-term exposure to $PM_{2.5}$ and lung function in children.

Copollutant Confounding

Several studies of pulmonary function in children provide information on potential copollutant confounding through the evaluation of two-pollutant models. These studies add to the strength of the evidence by establishing a $PM_{2.5}$ relationship with observed lung function decrements that is generally unchanged in models with other pollutants [quantitative results presented in Supplemental Material (U.S. EPA, 2018)]. $PM_{2.5}$ correlations with NO_2 ranged from 0.25 to 0.75, across studies. In studies that reported higher correlations (r = 0.75), associations between $PM_{2.5}$ and lung decrements were attenuated

but still negative in copollutant models adjusting for NO_2 (Wang et al., 2015b; Gehring et al., 2013). Meanwhile, in studies with low $PM_{2.5}$-NO_2 correlations ($r = 0.25–0.33$), associations were relatively unchanged in copollutant models (Chen et al., 2015a; Hwang et al., 2015). Hwang et al. (2015) and Chen et al. (2015a) also reported declines in lung function that persisted in copollutant models adjusting for CO, O_3, and SO_2. However, these studies of school-children in Taiwan lack generalizability given $PM_{2.5}$ concentrations that are much higher than studies in North America and Europe.

5.2.2.2.2 Adults

Lung function generally peaks in adults around the age of 25, and then slowly declines throughout adulthood (Götschi et al., 2008). In addition to studies of lung function in children, some studies have investigated whether long-term $PM_{2.5}$ exposure accelerates the rate of decline in lung function as adults age. A limited number of studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) observed contrasting evidence of an association between long-term exposure to $PM_{2.5}$ and lung function in adults. A longitudinal study of adults from 10 European countries found that annual $PM_{2.5}$ concentrations were not associated with lung function decrements measured from two spirometry tests taken approximately 10 years apart (Götschi et al., 2008). However, $PM_{2.5}$ exposures were estimated at the end of the study period, which may have introduced bias if the pattern of spatial variability of $PM_{2.5}$ concentrations did not remain constant across cities over the 10-year study period. In contrast, cross-sectional studies reported associations between annual average $PM_{2.5}$ and mean lung function (Schikowski et al., 2005; Ackermann-Liebrich et al., 1997). A limited number of recent longitudinal and cross-sectional studies in the U.S. and Europe have reported more consistent evidence that $PM_{2.5}$ is associated with decreased lung function parameters in adults. As with past studies, lung function in these cohorts was assessed either as a measure of lung function decline over time or cross-sectionally as a single measure in time. These cross-sectional measurements are generally less informative than longitudinal studies because they do not establish a temporal relationship between the exposure and outcome of interest. Study-specific details, air quality characteristics, and select results from these studies are presented in Table 5-20.

The Framingham Heart Study examined the association between long-term exposure to $PM_{2.5}$ and longitudinal decline in lung function over a 15-year period (Rice et al., 2015a). Rice et al. (2015a) reported a 5.25 ml/year (95% CI: 0.5, 10.5) faster rate of decline in FEV_1 and a 5 ml/year (95% CI: −0.25, 10.25) faster decline in FVC per 5 $\mu g/m^3$ increase in annual average $PM_{2.5}$ concentrations in the index year. The authors also observed $PM_{2.5}$ associations with cross-sectional FEV_1 and FVC measures but did not observe evidence of associations with FEV_1/FVC in longitudinal or cross-sectional analyses. In an ESCAPE project analysis of five European cohorts, Adam et al. (2015) also reported evidence of an association between long-term exposure to $PM_{2.5}$ and lung function in adults. Lung function measurements taken approximately 10 years apart indicated that long-term $PM_{2.5}$ exposure was associated with an accelerated decrease in FVC (−1.37 ml/year [95% CI: −4.04, 1.29]), but not FEV_1 (−0.14 ml,

95% CI [−2.26, 1.98]). However, similar to Götschi et al. (2008), discussed above, $PM_{2.5}$ was estimated (2008−2011) after the two spirometry tests were conducted (1985−2010). $PM_{2.5}$ was also negatively associated with cross-sectional FEV_1 and FVC levels measured during the second exam (Adam et al., 2015). Supporting evidence of a longitudinal association between $PM_{2.5}$ concentrations and lung function in adults, Boogaard et al. (2013) examined traffic policy-related reductions in air pollution and found improvements in lung function associated with declining $PM_{2.5}$ concentrations (Section 5.2.11).

In the Multi-Ethnic Study of Atherosclerosis (MESA), the association between long-term exposure to $PM_{2.5}$ and lung function was examined cross-sectionally (Adar et al., 2015). $PM_{2.5}$ was estimated using area-specific prediction models based on pollution measurements at the community or residential level in a subset of participants (MESA Air), which were incorporated with local geographic, meteorological, and emission data into a hierarchical spatiotemporal model to predict long-term exposure outside of participants' homes. $PM_{2.5}$ levels 1 year prior to baseline exam and 20-year average exposures were estimated and both were negatively associated with FEV_1 and FVC and with higher odds of airflow limitation. Similar to the Framingham Heart Study (Rice et al., 2015a), the authors found null associations between long-term exposure to $PM_{2.5}$ and FEV_1/FVC (Adar et al., 2015).

5.2.2.3 Summary of Lung Function and Development

In summary, recent epidemiologic studies enhance the evidence that was available in the 2009 PM ISA (U.S. EPA, 2009) suggesting that long-term exposure to $PM_{2.5}$ is associated with impaired lung function and lung function growth in children. Notably, extended CHS analyses continue to report $PM_{2.5}$-related decrements in lung development during the adolescent growth period. These updated analyses comprise additional cohorts with differing demographics and indicate that declining $PM_{2.5}$ concentrations are associated with improvements in lung development. Studies of attained lung function in children provide consistent evidence supporting the association observed with lung development. The strength of the epidemiology evidence was in the variety of exposure methods, study locations, and exposure levels for which associations were present. Additionally, a limited number of copollutant models indicate that the observed $PM_{2.5}$ effect may be independent of NO_2, CO, and O_3. The available evidence also indicates that $PM_{2.5}$ concentrations estimated proximate to lung function examination are most strongly associated with measures of attained lung function. These findings are supported by an animal toxicological study that demonstrated impaired lung development, as measured by decrements in lung function and changes in alveolar structure, as a result of pre- and post-natal exposure to $PM_{2.5}$. In a limited number of studies, altered nasal morphology and evidence of respiratory tract inflammation and oxidative stress were found in animals exposed to $PM_{2.5}$ during early lifestages.

While the 2009 PM ISA (U.S. EPA, 2009) noted inconsistent evidence of an association between long-term exposure to $PM_{2.5}$ and lung function in adults, more recent large prospective cohort studies have consistently observed $PM_{2.5}$-related accelerations of lung function decline in adults. This finding is

corroborated by evidence of lung function improvement in areas with declining $PM_{2.5}$ concentrations. Studies of lung function in adults have not adequately examined potential copollutant confounding.

5.2.3 Development of Asthma

Asthma is described by the National Heart, Lung, and Blood Institute as a chronic inflammatory disease of the airways that develops over time (NHLBI NAEPP, 2007). Pulmonary inflammation can increase airway responsiveness and induce airway remodeling, resulting in bronchoconstriction (bronchial smooth muscle contraction), and in turn, episodes of shortness of breath, coughing, wheezing, and chest tightness. When the pathophysiology of asthma advances in its development to the stage where the symptoms lead people to seek medical treatment, a diagnosis of asthma can result. A potential outcome of asthma development is that the pattern of reduced growth in lung function seen in early childhood persists into adulthood (McGeachie et al., 2016), potentially resulting in alterations to lung structure as adults (Donohue et al., 2013). In this section, asthma in children is discussed first, followed by asthma in adults, and subclinical effects underlying asthma development, such as pulmonary inflammation and increased airway responsiveness. While the evidence-base remains limited for subclinical effects and asthma in adults, recent studies of asthma in children supplement the limited number of studies reviewed in the 2009 PM ISA (U.S. EPA, 2009), and provide evidence of an association between long-term $PM_{2.5}$ exposure and asthma development in children.

5.2.3.1 Asthma in Children

Epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that examined asthma development in children were limited in number. In a birth cohort study in the Netherlands, early-life $PM_{2.5}$ exposure was associated with doctor-diagnosed asthma at age 4 years (Brauer et al., 2007). In the southern California Children's Health Study (CHS), $PM_{2.5}$ was examined in relation to the association between lung function and asthma incidence. The protective association between lung function and new onset asthma observed in the overall population was not present in high $PM_{2.5}$ communities (Islam et al., 2007).

The recent body of literature enhances the limited evidence base, providing further evidence that long-term exposure to $PM_{2.5}$ is associated with asthma development in children. The strongest evidence supporting the relationship between long-term exposure to $PM_{2.5}$ and childhood asthma comes from a number of recent prospective and retrospective cohort studies conducted in North America and Europe. Longitudinal epidemiologic studies, which follow subjects over time, can better characterize the temporal sequence between $PM_{2.5}$ exposures and the incidence of asthma by ascertaining the first record of a physician diagnosis. In this regard, longitudinal studies distinguish between asthma onset and asthma exacerbation. Study-specific details, air quality characteristics, and select results from these studies,

discussed throughout this section, are highlighted in Table 5-21. In the majority of studies, asthma incidence was ascertained through validated questionnaires that asked parents about the child ever having a physician diagnosis of asthma at baseline, and, at each follow-up, questions about a diagnosis of asthma in the intervening period. In other studies, asthma was assessed by pediatric allergist evaluation (Carlsten et al., 2011) and primary care physician diagnosis or hospitalization due to asthma (Tétreault et al., 2016a; Clark et al., 2010).

Most recent asthma incidence studies focus on birth year as the period of potentially heightened sensitivity to $PM_{2.5}$ exposure and examine asthma incidence across varying follow-up times. The association between birth-year $PM_{2.5}$ exposure and diagnosis of asthma at age 7 was examined in a birth cohort of children at high-risk for asthma (n = 186) in Vancouver, Canada (Carlsten et al., 2011). The smaller sample size compared to other recent studies is balanced by using a high-risk cohort, which results in a higher proportion of cases compared to general population studies. Despite low mean outdoor $PM_{2.5}$ concentrations at birth residences (5.6 $\mu g/m^3$), Carlsten et al. (2011) observed that $PM_{2.5}$ was associated with increased odds of asthma diagnosis (OR: 4.0 [95% CI: 1.4, 11.5). In a larger study with relatively low mean $PM_{2.5}$ concentrations (9.9 $\mu g/m^3$; max: 14.9), Tétreault et al. (2016a) reported a positive and precise association between $PM_{2.5}$ and onset of asthma in an administrative cohort study of over 1 million children (HR: 1.23 [95% CI: 1.21 to 1.24]). The observed HR was robust to sensitivity analyses examining the impact of time-varying $PM_{2.5}$ concentrations and more rigorous case definitions for children under 5. Other studies conducted at higher $PM_{2.5}$ concentrations also reported generally positive associations between $PM_{2.5}$ and asthma incidence (Figure 5-30). A pooled retrospective case-control analysis of minority children provided an exception to the generally consistent evidence of an association (Nishimura et al., 2013). However, the study had low statistical power due to missing $PM_{2.5}$ concentration measurements for some regions.

Table 5-21 Longitudinal studies of long-term $PM_{2.5}$ exposure and asthma incidence in children.

Study	Study Population	Exposure Assessment	Effect estimates 95% CI[a]	Copollutant Examination
Brauer et al. (2007) The Netherlands 1997–2001 Prospective cohort	PIAMA n = 3,934 Follow-up: At 4 yr old 85.3% follow-up participation at 4 yr	GIS model Long-term avg $PM_{2.5}$ concentration for the first 4 yr of life Mean: 16.9 µg/m^3 Max: 25.2 µg/m^3	OR: 1.6 (1.1, 2.2)	Correlation (*r*): 0.96 NO_2 Copollutant models with: NA
†Carlsten et al. (2011) Vancouver, Canada 1995–2002 Prospective cohort	CAPPS: A high-risk asthma birth cohort n = 184 Follow-up: At 7 yr old 63% follow-up participation at 7 yr	Annual avg $PM_{2.5}$ concentration estimated at birth residence (birth year) using LUR. Mean: 5.6 µg/m^3	OR: 4.0 (1.4, 11.5)	Correlation (*r*): 0.7 NO_2 Copollutant models with: NA
†Gehring et al. (2010) The Netherlands 1996–2004 Prospective cohort	PIAMA n = 3,863 Follow-up: Annually from birth to 8 yr 94.4% participation at Yr 1, 82% at Yr 8	Annual avg $PM_{2.5}$ concentration estimated at birth residence (birth year) using LUR. Cross-validation RMSE for validation 1.59 µg/m^3; Model R^2 = 0.78 Mean: 17.5 µg/m^3 Max: 25.7 µg/m^3	Without adjustment for study region OR: 1.5 (1.2, 1.9) With adjustment for study region OR: 1.4 (0.95, 2.1)	Correlation (*r*): 0.93 NO_2 Copollutant models with: NA
†Gehring et al. (2015a) The Netherlands 1996–2008 Prospective cohort	PIAMA n = 3,702 children Follow-up: Annually from birth to 8 yr and again at age 11–12 yr	Annual avg $PM_{2.5}$ concentration estimated at birth residence (birth year) and current address (at time of questionnaire) using LUR. LOOCV R^2 = 0.61 Median: 16.5 µg/m^3 75th: 25.3 µg/m^3 95th: 26.4 µg/m^3	Birth address OR: 1.6 (0.9, 2.9) Current address OR: 1.2 (0.6, 2.4) (Birth address $PM_{2.5}$ vs current address $PM_{2.5}$ correlation (*r*): 0.74)	Correlation (*r*): 0.73 NO_2 (at birth address) Copollutant models with: NA
†Yang et al. (2016) The Netherlands 1996–2011 Prospective cohort	PIAMA n = 3,701 children Follow-up: Annually from birth to 8 yr and again at age 11–12 yr and 14 yr	Annual avg $PM_{2.5}$ concentration estimated at birth residence (birth year) and current address (at time of questionnaire) using LUR. LOOCV R^2 = 0.61; Model R^2 = 0.67	Birth address OR: 1.4 (0.8, 2.5) Current address OR: 1.1 (0.6, 2.0)	Correlation (*r*): NA Copollutant models with: NA

Table 5-21 (Continued): Longitudinal studies of long term $PM_{2.5}$ exposure and asthma incidence in children.

Study	Study Population	Exposure Assessment	Effect estimates 95% CI[a]	Copollutant Examination
†MacIntyre et al. (2014a) Vancouver, Canada; Munich and Wesel, Germany; the Netherlands; and East and West Germany. Pooled analysis of prospective cohorts.	TAG: A pooled analysis of CAPPS Vancouver, PIAMA, LISA, and GINI birth cohorts N = 2,743	Annual avg $PM_{2.5}$ concentration estimated at birth residence (birth year) using LUR. For LISA/GINI R^2 = 0.56; RMSE for model validation: 1.35 µg/m^3 Model validation for CAPPS and PIAMA as noted above Mean: 15.2 µg/m^3 Max: 25.1 µg/m^3	Current asthma OR: 2.5 (1.5, 4.3) Ever asthma OR: 1.2 (0.8, 1.8)	Correlation (*r*): 0.23 NO_2 Copollutant models with: NO_2
†Gehring et al. (2015b) Sweden, Germany, and the Netherlands. Pooled and meta-analyses of prospective cohorts	BAMSE, PIAMA, LISA, and GINI n = 14,126 Followed to 14 −16 yr of age	LUR was used to estimate annual avg $PM_{2.5}$ concentrations at the participant's birth and current home addresses. Model R^2 BAMSE: 87%; GINI/LISA North: 83%; GINI/LISA South: 69%; and PIAMA: 67%. $PM_{2.5}$ concentrations at birth address Mean across cohorts: 7.8 to 17.4 µg/m^3	Random-effects meta-analysis Birth year OR: 1.3 (0.9,1.7) Current address OR: 1.1 (0.9, 1.5)	Correlation with NO_2 "high". Quantitative results not reported. Copollutant models with: NA
†Mcconnell et al. (2010) Southern California 2002−2006 Prospective cohort	CHS n = 2,497 children; ages 4.8−9.0 yr at enrollment Follow-up: 3 yr 74% follow-up participation	Annual avg $PM_{2.5}$ concentration from one fixed-site monitor per community. Concurrent exposure.	HR: 1.2 (0.97, 1.4)	Correlation (*r*): NA Copollutant models with: NA
†Clark et al. (2010) Southwest British Columbia, Canada 1999−2004 Prospective case control	British Columbia population-based birth cohort n = 20,130 Follow-up: 3−4 yr to diagnosis by age 4 yr	LUR model used to estimate annual avg $PM_{2.5}$ concentration at birth residence for 1st-year and in utero exposure. Also assessed exposure concentration estimated by $PM_{2.5}$ concentrations at industrial point sources using an IDW However, there was no association for prenatal exposure estimated by an IDW summation of emissions from point sources. Mean: LUR 4.5 µg/m^3 IDW 5.62 µg/m^3	Prenatal IDW: 0.8 (0.6, 1.0) LUR: 1.1 (1.0, 1.2) First year IDW: 1.3 (0.9, 1.9) LUR: 1.1 (0.95, 1.2)	Correlations among pollutants were stated to be generally high. Quantitative results not reported. Copollutant models with: NA

Table 5-21 (Continued): Longitudinal studies of long term $PM_{2.5}$ exposure and asthma incidence in children.

Study	Study Population	Exposure Assessment	Effect estimates 95% CI[a]	Copollutant Examination
†Nishimura et al. (2013) Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA; Puerto Rico. Retrospective case-control	GALA II and SAGE II n = 948 Ages 8–21 yr	Average $PM_{2.5}$ concentration for 1st yr and first 3 yr of life estimated using IDW of four closest monitors within 50 km of birth residence. Mean across cities: 8.1 to 17.0 µg/m^3	First year of life exposure All cities combined: 1.2 (0.6, 2.3) [Houston: 1.2 (0.6, 15.5); Puerto Rico: 1.6 (0.8, 3.3); Chicago: 0.5 (0.1, 1.6); New York: 3.7(1.0, 13.7) San Francisco (GALA): 0.4(0.1 to 1.8); San Francisco (SAGE): 0.7 (0.2, 2.4)]	Correlation (*r*): NA Copollutant models with: NA
†Tétreault et al. (2016a) Quebec, Canada 1996–2011	The Quebec Integrated Chronic Disease Surveillance System was used to create an open birth cohort n = 1,183,865	Mean $PM_{2.5}$ concentrations at birth address estimated at the postal code scale during 2001–2006 derived using satellite imagery and a CTM, Concentrations were assumed to be constant throughout the study period. Mean: 9.86 µg/m^3 Max: 14.85 µg/m^3	Birth address HR: 1.23 (1.21 to 1.24)	Correlation (*r*): NA Copollutant models with: NA

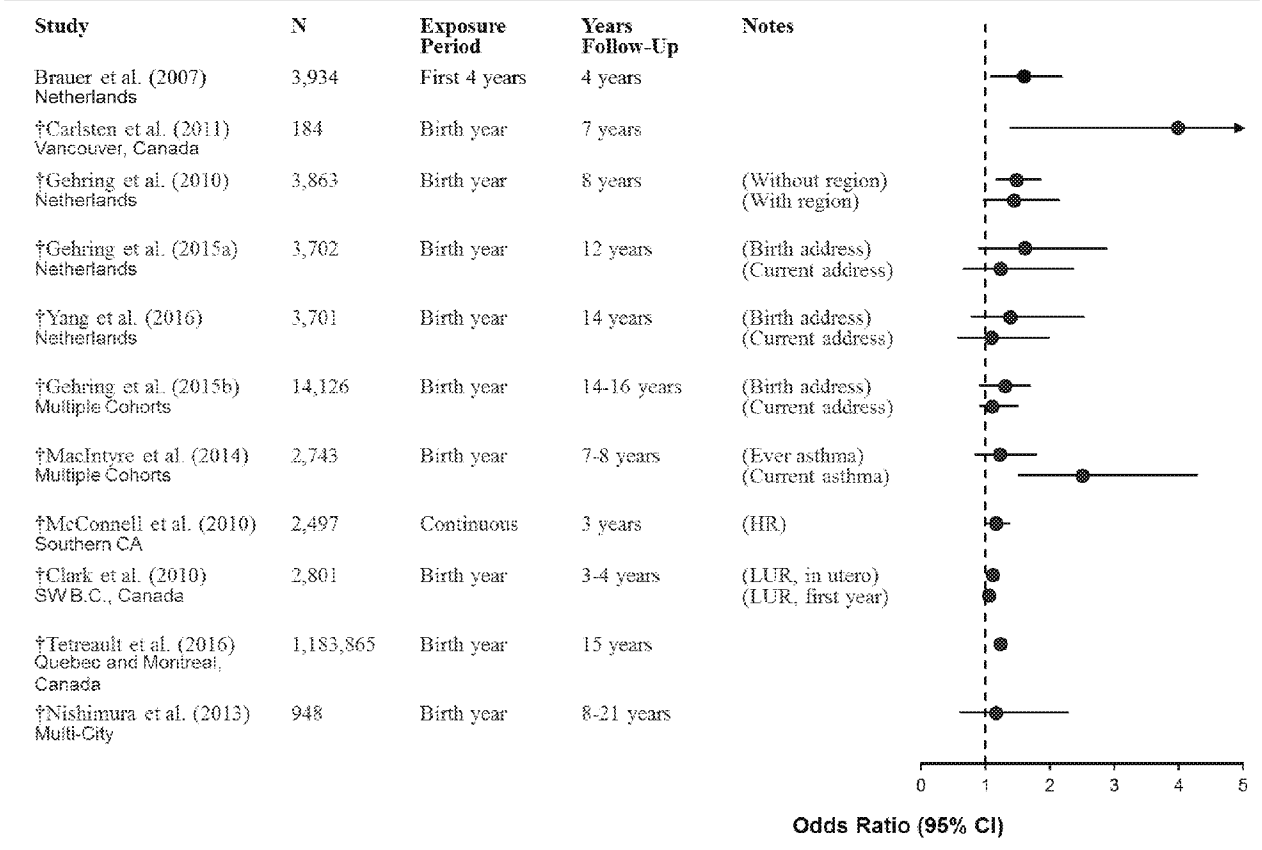
BAMSE = The Children, Allergy, Milieu, Stockholm, Epidemiological Survey, CAPPS = Canadian Asthma Primary Preventions Study, CHS = Children's Health Study, GALA II = Genes environments and Admixture in Latino Americans, GINI = German Infant Nutrition Intervention Study, GIS = geographic information system, HR = hazard ratio, IDW = inverse distance weighting, IQR = interquartile range, LISA = Lifestyle Factors on the Development of the Immune System and Asthma, LOOCV = leave one out cross-validation, NO = nitric oxide, NO_2 = nitrogen dioxide, NR = not reported, OR = odds ratio, PIAMA = Prevention and Incidence of Asthma and Mite Allergy, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, RMSE = root mean square error, SAGE II = Study of African Americans, Asthma, Genes, and Environments, SD = standard deviation, TAG = The Traffic, Asthma and Genetics study, CTM = chemical transport model.

[a]Effect estimates are standardized to a 5 µg/m^3 increase in $PM_{2.5}$.

†Studies published since the 2009 PM ISA.

A number of studies examined alternate exposure windows to assess other periods of potential sensitivity to PM exposure in the development of asthma. Two studies of the PIAMA cohort in the Netherlands (Yang et al., 2016; Gehring et al., 2015a), and one pooled analysis of four European birth cohorts (Gehring et al., 2015b), observed that asthma incidence was associated with $PM_{2.5}$ concentrations outside birth residences, and reported attenuated but still positive associations with $PM_{2.5}$ concentrations at the address of the participant at the time of follow-up (quantitative results presented in Table 5-21). As

discussed in Section 5.2.2.2.1, exposure was modeled after follow-up for all of these cohorts, such that exposure estimates are representative of spatially relative concentrations. An earlier PIAMA study stratified by participants who had and had not moved from their birth address (movers vs. nonmovers) and observed associations between $PM_{2.5}$ and incident asthma that were slightly stronger in magnitude in nonmovers (OR: 1.6 [95% CI: 1.1, 2.3]) than movers (OR: 1.3 [95% CI: 0.97, 1.8]) (Gehring et al., 2010). While the difference in ORs is not large, the stratified results may suggest continued sensitivity to $PM_{2.5}$ exposure later in life. In a nested case-control study in British Columbia, Clark et al. (2010) examined asthma incidence at ages 3–4 years in association with $PM_{2.5}$ concentrations in both the prenatal period and first year of life. The authors reported similar asthma-$PM_{2.5}$ associations for prenatal and first year of life exposures estimated by LUR (OR [95% CI]: 1.1 [1.0, 1.2] and 1.1 [0.95, 1.2] for prenatal and first year $PM_{2.5}$ averages, respectively).



CI = confidence interval, HR = hazard ratio, LUR = land use regression.

Note: †Studies published since the 2009 PM ISA. Black text/circles = studies evaluated in the 2009 PM ISA. Red text/circles = studies published since the completion of the 2009 PM ISA. Odds ratios are standardized to an increment of 5 $\mu g/m^3$. Corresponding quantitative results and study details are reported in Table 5-21.

Figure 5-30 Long-term exposure to $PM_{2.5}$ and asthma incidence in children.

Recent studies of asthma prevalence generally provide supporting evidence for an association with $PM_{2.5}$ (Hasunuma et al., 2014 Macintyre, 2014, 2230511, Gehring, 2015, 3070314; Mölter et al., 2014), though some did not (Fuertes et al., 2013b; Akinbami et al., 2010). Supporting evidence was also reported in studies examining $PM_{2.5}$ and wheeze, a common symptom of asthma. Repeated wheeze in 2-year-olds was prospectively studied in a pregnancy cohort of women (n = 708) receiving care at Brigham & Women's Hospital in Boston (Chiu et al., 2014). Prenatal $PM_{2.5}$ exposure, estimated using a hybrid model incorporating AOD observations with land use predictors to yield residence-specific ambient $PM_{2.5}$ concentration estimates, was associated with increased odds of repeated wheeze at age 2 (OR: 2.0 [95% CI: 1.2, 3.4] for above median vs. below median $PM_{2.5}$ concentrations). In the larger PIAMA cohort study detailed in Table 5-21, Gehring et al. (2010) observed increased odds of parental-reported prevalent wheeze during the first 8 years of life associated with long-term $PM_{2.5}$ concentration (OR: 1.3 [95% CI: 1.1, 1.6]).

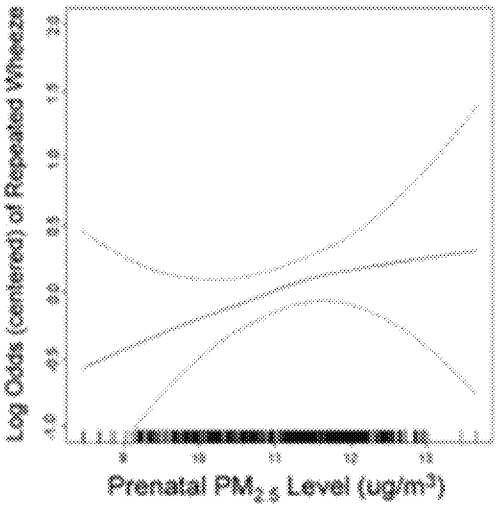
5.2.3.1.1 Copollutant Confounding

Most of the reviewed studies of asthma incidence in children did not present results from copollutant models. This may be the result of consistently high correlations reported between $PM_{2.5}$ and other pollutants across studies (Table 5-21), which reduces the reliability of copollutant models. MacIntyre et al. (2014a) observed a weak correlation between $PM_{2.5}$ and NO_2 ($r = 0.23$) in a pooled analysis of four birth cohorts. The association observed between birth-year $PM_{2.5}$ exposure and having a current asthma diagnosis (OR [95% CI]: 2.5 [1.5, 4.3]) remained after adjustment for NO_2 in a copollutant model (4.5 [1.4, 14.2]). However, given the lack of additional studies, uncertainties remain regarding whether the association between $PM_{2.5}$ and asthma incidence in children is independent of coexposure to other pollutants.

5.2.3.1.2 Concentration-Response Relationship

The shape of the C-R relationship between asthma incidence in children and long-term exposure to $PM_{2.5}$ was examined in (Tétreault et al., 2016a). To examine whether there is evidence of linearity in the relationship restricted cubic splines with three knots were included in the model. For $PM_{2.5}$, as well as O_3 and NO_2, nonlinear models did not result in better fits than the linear models for both exposures outside the home address at birth and for time-varying exposures during the follow-up period. Carlsten et al. (2011) examined the $PM_{2.5}$-asthma incidence association across exposure quartiles and reported monotonically increasing risk. However, this analysis stratified an already small sample size, resulting in wide CIs for each quartile estimate of risk. A C-R relationship was also evaluated in a study of childhood wheeze. Chiu et al. (2014) used penalized spline models to assess the nature of the relationship between prenatal $PM_{2.5}$ exposure and repeated wheeze. As depicted in Figure 5-31, the C-R relationship was approximately linear with some evidence of a less steep relationship at the higher exposure levels, albeit

with high uncertainty due to limited data at higher exposures. Confidence in the shape of the curve, as indicated by the dotted lines surrounding the spline curve, is highest from about 10 to 12 μg/m^3, where most of the observations occur. None of the evaluated studies provide a thorough empirical evaluation of alternatives to linearity, limiting the conclusions that can be drawn with respect to the shape of the C-R relationship.



Solid lines depict the penalized spline curve, and dotted lines indicate the 95% confidence bounds.
Source: Permission pending, Chiu et al. (2014).

Figure 5-31 Concentration-response relationship of prenatal $PM_{2.5}$ with children's repeated wheeze.

5.2.3.2 Asthma in Adults

No studies of long-term $PM_{2.5}$ exposure and asthma in adults were discussed in the 2009 PM ISA (U.S. EPA, 2009). Since then, a number of recent studies have examined incidence and prevalence of asthma and wheeze in adults in several cohorts. Contrary to the recent evidence supporting the presence of an association in children, the results for adult populations have been largely inconsistent. Study-specific details, including study locations, cohort descriptions, air quality characteristics, and select results from these studies, are highlighted in Table 5-22. A forest plot of the effect estimates, depicting the heterogeneity of results across studies, is presented in Figure 5-32.

Table 5-22 Long-term $PM_{2.5}$ exposure and asthma and wheeze incidence and prevalence in adults.

Study	Study Population	Exposure Assessment	Effect estimates (95% CI) per 5 µg/m^3	Copollutant Examination
Asthma incidence				
†Young et al. (2014) U.S. 2003–2012 Prospective cohort	The Sister Study; cohort of women with at least one sister with a diagnosis of breast cancer. n = 39,350 Enrollment from 2003–2006. Follow-up from 2008–2012 (Participation >99%)	Kriging regression monitor values using geographic variables. Annual avg $PM_{2.5}$ concentration estimated outside home address at enrollment. Cross-validated R^2: 0.88 Mean: 10.8 µg/m^3 Range: 1.9–18.0 µg/m^3	Incident asthma OR: 1.3 (0.99, 1.7) Incident wheeze OR: 1.2 (1.1, 1.4)	Correlation (*r*): NA Copollutant models with: NA
†To et al. (2015) Ontario, Canada 1980–2003 Prospective cohort	The Canadian National Breast Screening Study n = 29,549 women, ages 40–59 at enrollment Enrollment from 1980–1985. Follow-up using administrative databases from 1992–2003	Long-term avg $PM_{2.5}$ concentrations from 1998–2006 estimated at 10 ×10 km grid level using AOD observations from satellite imagery. R^2 with ground monitors: 0.77 Mean (SD): 12.47 (2.40) µg/m^3	RR: 1.0 (0.92, 1.25)	Correlation (*r*): NA Copollutant models with: NA
†Jacquemin et al. (2015) 24 European Cities Combination of six prospective cohorts	The European Study of Cohorts for Air Pollution Effects n = 17,098	LUR models of annual avg $PM_{2.5}$ concentration at participants' address at follow-up. Range of means across cities: 10 to 18 µg/m^3	OR: 1.0 (0.88, 1.2)	Correlation (*r*): (range across cities) 0.60–0.90 NO_2; 0.51–0.94 NO_X; 0.63–0.88 PM_{10}; 0.22–0.67 $PM_{10-2.5}$ Copollutant models with: NA Copollutant models NR

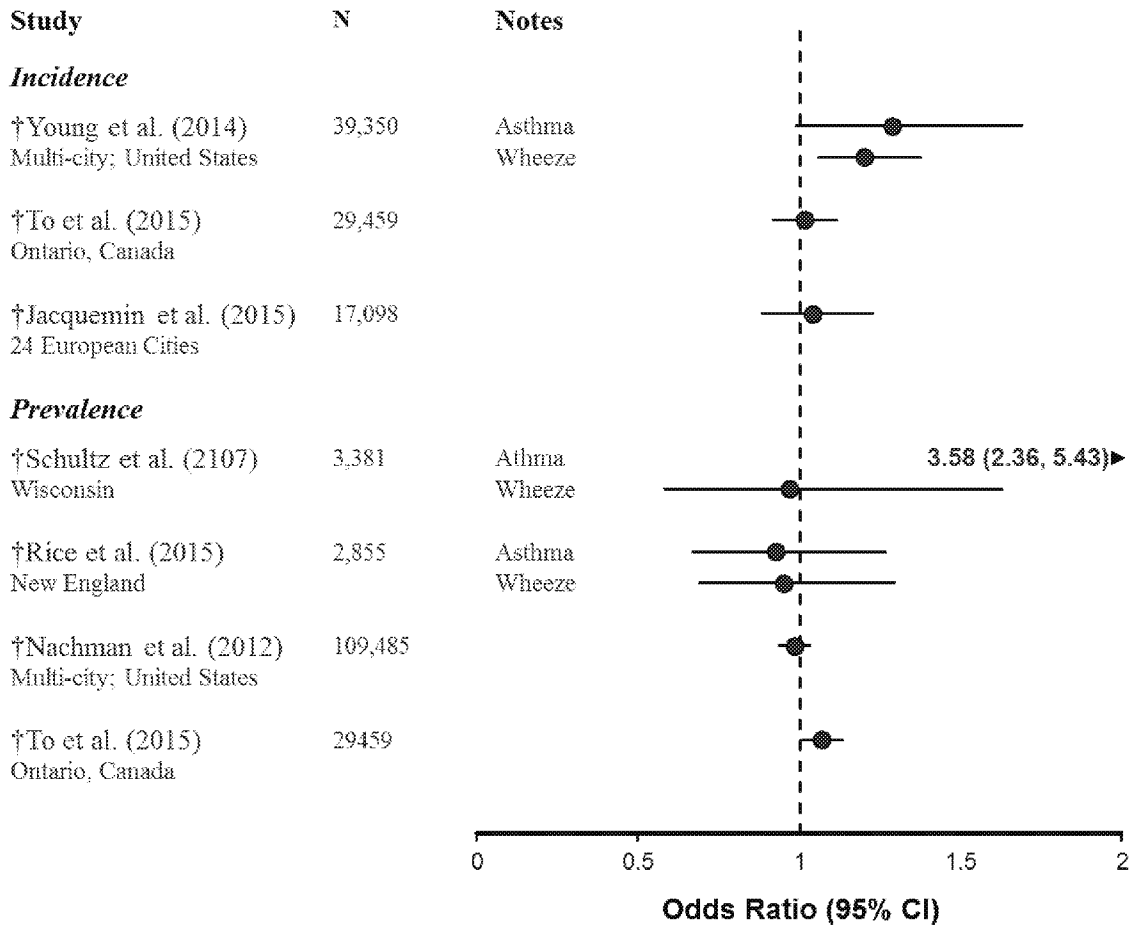
Table 5-22 (Continued): Long term $PM_{2.5}$ exposure and asthma and wheeze incidence and prevalence in adults.

Study	Study Population	Exposure Assessment	Effect estimates (95% CI) per 5 µg/m^3	Copollutant Examination
Asthma prevalence				
†Schultz et al. (2017) Wisconsin 2008–2013 Cross-sectional	Survey of the Health of Wisconsin (SHOW); probabilistic survey design n = 3,381 adults ages 21+	Annual avg $PM_{2.5}$ concentration estimates from U.S. EPA Bayesian space-time downscaler. 12 × 12 km gridded estimates were linked to participants' home addresses. 1-yr lag. 5th: 10.9 µg/m^3 Max: 15.1 µg/m^3	Prevalent asthma OR: 3.6 (2.4, 5.4) Prevalent wheeze OR: 0.97 (0.58, 1.6)	Correlation (*r*): NA Copollutant models with: NA
†Rice et al. (2015a) New England Enrollments Offspring: 1971–1975 Third generation: 2002–2005 Cross-sectional analysis of longitudinal data	Framingham Offspring and Third Generational Cohorts n = 2,855 Biennial follow-up	Annual avg $PM_{2.5}$ concentrations for 2001 were estimated at 10 × 10 km grid level using AOD observations from satellite. Resolved to 50 × 50 m using land use terms and assigned to participants' home addresses. 10-fold cross-validated LOOCV R^2: 0.85 Mean: 10.8 µg/m^3 Max: 21.7 µg/m^3	Prevalent asthma OR: 0.93 (0.67, 1.3) Prevalent wheeze OR: 0.95 (0.68, 1.3)	Correlation (*r*): NA Copollutant models with: NA
†Nachman and Parker (2012) U.S. 2002–2005 Cross-sectional	National Health Interview Survey (NHIS); multistage probability survey n = 109,485 adults ages 18+	Annual avg $PM_{2.5}$ concentrations were estimated from a kriging model used to interpolate monitor concentrations. Median: 12.6 µg/m^3 Max: 24.7 µg/m^3	OR: 0.99 (0.93, 1.03)	Correlation (*r*): NA Copollutant models with: NA
†To et al. (2015) See details above	See details above	See details above	RR: 1.1 (1.0, 1.3)	See details above

LOOCV = leave one out cross-validation, NO = nitric oxide, NO_2 = nitrogen dioxide, NR = not reported, OR = odds ratio; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, RR = relative risk, SD = standard deviation.

[a]Effect estimates are standardized to a 5 µg/m^3 increase in $PM_{2.5}$.

†Studies published since the 2009 PM ISA.



CI = confidence interval.

Note: †Studies published since the 2009 PM ISA. Black text/circles = studies evaluated in the 2009 PM ISA. Red text/circles = studies published since the completion of the 2009 PM ISA. Odds ratios are standardized to an increment of 5 $\mu g/m^3$. Corresponding quantitative results and study details are reported in Table 5-22.

Figure 5-32 Asthma and wheeze incidence and prevalence in adults in relation to long-term $PM_{2.5}$ exposure.

A limited number of studies on incident asthma in adults reported inconsistent evidence of an association. In a large prospective cohort study of women across the U.S., asthma incidence was associated 1-year average $PM_{2.5}$ concentrations at the beginning of follow-up (OR: 1.3 [95% CI: 0.99, 1.7]) (Young et al., 2014). Cases were defined by self-reporting of all three of the following conditions: asthma diagnosis by a doctor, use of asthma medication, and presence of asthma symptoms. In support of the association seen with incident asthma, Young et al. (2014) also reported an increase in wheeze incidence associated with long-term exposure to $PM_{2.5}$. In contrast, the ESCAPE study, an analysis of six

European cohorts, did not observe an association between long-term $PM_{2.5}$ concentrations and asthma onset in adults (Jacquemin et al., 2015). The finding was unchanged in a sensitivity analysis aimed at reducing exposure measurement error by restricting the analysis to cities with better LUR model validation. Similarly, in a large cohort study of chronic disease prevalence in women living in Ontario, Canada, To et al. (2015) also reported a null association. However, because $PM_{2.5}$ concentrations were estimated from satellite observations of AOD taken in the middle of the study period, asthma cases were restricted to the years after exposure estimates were available, which reduced the case number and power of the study. Utilizing the entire study population, To et al. (2015) did observe an association between long-term $PM_{2.5}$ exposure and asthma prevalence.

In addition to the To et al. (2015) study, there were a few other studies that examined asthma prevalence in adults. These studies were of cross-sectional design and the results, similar to studies of asthma incidence, were also inconsistent. While a health survey-based study of adults in Wisconsin reported evidence of a large increase in odds of asthma prevalence in association with annual average $PM_{2.5}$ concentration in the previous year (OR [95% CI]: 3.58 [2.36, 5.43]), the authors did not observe an association with prevalent wheeze (Schultz et al., 2017). In contrast, cross-sectional analyses of a longitudinal cohort (Rice et al., 2015a) and a national health survey (Nachman and Parker, 2012) observed null associations between long-term exposure to $PM_{2.5}$ and asthma prevalence in adults.

5.2.3.3 Subclinical Effects Underlying Development of Asthma

Subclinical effects underlying the development of asthma, including airway inflammation and airway hyperresponsiveness, have been examined in both epidemiologic studies and animal toxicological studies. The 2009 PM ISA (U.S. EPA, 2009) reported a cross-sectional analysis of school children in Windsor, Ontario that observed an increase in airway inflammation (eNO) corresponding to an increase in annual $PM_{2.5}$ concentrations (Dales et al., 2008). Also reviewed in the 2009 PM ISA were several studies that reported subclinical effects underlying the development of asthma following long-term exposure to DE or woodsmoke. However, these studies did not distinguish between effects due to gases or particles in the mixture.

5.2.3.3.1 Epidemiologic Studies

Recently, a longitudinal study of the CHS cohort reported that, in models adjusted for short-term $PM_{2.5}$ exposure, annual $PM_{2.5}$ concentrations were associated with a 10.3 ppb (95% CI: 3.0, 17.6) increase in FeNO (Berhane et al., 2014). Results from a prior CHS analysis (Bastain et al., 2011) showed that elevated eNO was associated with increased risk of new onset asthma. However, potential copollutant confounding was not examined in either study. Thus, there are a limited number of epidemiologic studies

providing evidence for subclinical effects underlying the development of asthma in association with long-term exposure to $PM_{2.5}$.

5.2.3.3.2 Animal Toxicological Study

Recently, a study evaluating the effects of $PM_{2.5}$ on the development of asthma has become available. Kim et al. (2016a) exposed BALB/c mice to nebulized DEPs for 4, 8, and 12 weeks and found increased BALF levels of the Th2 cytokines IL-5 (8 and 12 weeks) and IL-13 (4 and 12 weeks) ($p < 0.05$). Since these mice were naïve and not sensitized or challenged with allergens, this result provides evidence that $PM_{2.5}$ can induce an immune phenotype in the absence of an allergen. In addition, airway responsiveness to methacholine was assessed using whole-body plethysmography to measure Penh. Methacholine is a muscarinic receptor agonist that elicits bronchoconstriction and is used to evaluate airway hyperresponsiveness, a hallmark of asthma. DEP exposure resulted in increased Penh at all three-time points studied ($p < 0.01$). As discussed in Section 5.1.2.3.3, there is uncertainty associated with the use of Penh for the determination of airway responsiveness. Additional study details are found in Table 5-23.

Table 5-23 Study-specific details from an animal toxicological study of long-term $PM_{2.5}$ exposure and subclinical effects underlying development of asthma.

Study/Study Population	Pollutant	Exposure	Endpoints
Kim et al. (2016a) Species: Mouse Strain: BALB/c Sex: Female Age/Weight: 5–6 weeks	DEP nebulized Particle size: Mean diameter 0.4 µm before nebulization and 1–5 µm after nebulization Control: Saline solution	Dose/Concentration: 0.1 and 3 mg/m^3 DEP or saline (Only results from 0.1 mg/m^3 reported here) Duration: 1 h/day, 5 days/week for 4, 8, and 12 weeks Time to analysis: 1 day after last exposure	Penh- methacholine challenge BALF cells BALF cytokines Histochemistry • Masson trichome staining of lung

DEP = diesel exhaust particles; Penh = enhanced pause.

5.2.4 Development of Allergic Disease

The 2009 PM ISA (U.S. EPA, 2009) reviewed a limited number of epidemiologic studies examining a range of allergic indicators that found a mix of positive and null associations with long-term exposure to $PM_{2.5}$. While a number of studies reported $PM_{2.5}$ associations with hay fever/allergic rhinitis, indoor and outdoor allergic sensitization, and/or eczema, there was comparable evidence of null

associations across the same endpoints within the reviewed studies. Most studies examining allergic endpoints assessed prevalence outcomes cross-sectionally. In addition to a lack of prospective studies on allergic disease incidence, none of the studies reviewed in the 2009 PM ISA used copollutant models to evaluate the independent effect of $PM_{2.5}$. Studies published since the completion of the 2009 PM ISA encompass two main indicators of allergic disease: hay fever/allergic rhinitis diagnosis and allergic sensitization. In addition, a single recent animal toxicological study provided evidence that long-term $PM_{2.5}$ exposure can promote the development of a Th2 phenotype (see Section 5.2.3.3.2).

Allergic sensitization, measured by detectable allergen-specific IgE levels, was examined in the recent evidence base. A pooled analysis of five European birth cohorts reported that annual average $PM_{2.5}$ concentrations outside participants' birth addresses were associated with higher odds of sensitization to any common allergen at ages 4 and 8 (Gruzieva et al., 2014). However, the association was driven by results from the PIAMA cohort in the Netherlands (Gehring et al., 2010), whereas analyses of other cohorts included in the pooled analysis, such as the LISA and GINI cohorts (Fuertes et al., 2013b), did not observe associations. The PIAMA cohort study observed associations with $PM_{2.5}$ concentrations outside birth addresses that were larger in magnitude compared to current addresses, but also reported associations that were larger in magnitude among nonmovers compared to movers (Gehring et al., 2010). As discussed in Section 5.2.3 on asthma development, early life exposure may be important to allergic sensitization, but the critical exposure window may continue into later childhood. In a 2005–2006 NHANES study comprising a nationally representative sample of the U.S. population, Weir et al. (2013) found that annual average $PM_{2.5}$ concentration was associated with increased odds of sensitization to indoor allergens for exposure assigned from monitors within 20 miles of the participants' home address (OR: 1.27 [95% CI: 1.12, 1.45]) and using geocoded CMAQ $PM_{2.5}$ concentration estimates (OR: 1.26 [95% CI: 1.16, 1.38]). Associations with sensitization to food allergens were positive but imprecise, while sensitization to outdoor allergens were not related to annual average $PM_{2.5}$ concentrations. Although copollutant models were not examined, $PM_{2.5}$ was weakly correlated with NO_2 and O_3.

Other recent studies examined parental and self-reported hay fever/allergic rhinitis and rhino conjunctivitis in children and adults. A few studies of the PIAMA cohort reported that $PM_{2.5}$ assigned at birth address was not associated with increased odds of hay fever (Gehring et al., 2010) or rhino conjunctivitis incidence (Gehring et al., 2015b) in children. However, an association of $PM_{2.5}$ with hay fever was present in children who did not move during follow-up (OR [95% CI]: 1.43 [1.01, 2.04]). The lack of an association in the overall population may have been due to exposure measurement error for children who moved, as evident in the association amongst nonmovers. In contrast to Gehring et al. (2010), a pooled analysis of six Canadian and European cohorts (CAPPS, SAGE, PIAMA, BAMSE, and GINI/LISA), reported that birth-year $PM_{2.5}$ was associated with a 37% increase in odds of allergic rhinitis at age 7–8 (95% CI: 1, 86%) (Fuertes et al., 2013a). Wang et al. (2015a) also observed a positive association between parental-reported allergic rhinitis and cumulative long-term $PM_{2.5}$ exposure in a cohort of kindergarteners living within 10 km of an air quality monitoring station. In a cross-sectional study of adults in Wisconsin, Schultz et al. (2017) observed no evidence of a linear association between

annual $PM_{2.5}$ concentrations and subjects who self-reported a physician diagnosis of allergies or hay fever (OR: 1.06 [95% CI: 0.74, 1.53]). However, the authors reported increased odds of allergies or hay fever for participants in the second (9.32−10.20 μg/m^3; OR: 1.38 [95% CI: 1.03, 1.76]) and third (10.21−10.85 μg/m^3; OR: 1.33 [95% CI: 1.00, 1.76]) quartiles of PM exposure compared to those in the first (6.59−9.31 μg/m^3), suggesting a potential nonlinear association.

In summary, recent studies evaluated associations between long-term exposure to $PM_{2.5}$ and various allergic outcomes in a mix of large representative cohort and cross-sectional survey studies. While recent evidence includes more longitudinal study designs, there are no studies that evaluate copollutant models. Despite this limitation, there is generally consistent evidence of an association between long-term $PM_{2.5}$ exposure and allergic sensitization in single pollutant models. However, as seen in Weir et al. (2013) and studies reviewed in the 2009 PM ISA (U.S. EPA, 2009), consistent associations with specific allergens have not emerged. The findings for allergic rhinitis were inconsistent, although a limited number of studies that aimed to reduce exposure measurement error, either by restricting distance between study participants and monitors or by excluding participants who moved, did observe associations. Overall, evidence indicates an association between long-term exposure to $PM_{2.5}$ and at least some manifestations of allergic disease. Limited evidence from a single animal toxicological study showing that long-term exposure to DEP promotes the development of an allergic phenotype supports for epidemiologic findings of allergic responses.

5.2.5 Development of Chronic Obstructive Pulmonary Disease (COPD)

There were no epidemiologic studies examining the association between long-term exposure to $PM_{2.5}$ and COPD available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). An animal toxicological study provided evidence for the development of emphysema, a form of COPD, following long-term exposure to woodsmoke, but did not distinguish between effects due to gases or particles in the mixture. Several recent epidemiologic studies examined COPD as an outcome using medical records data, lung function measures, and imaging data obtained in cohorts and cross-sectional studies based in North America and Europe. Studies also examined specific forms of COPD, including emphysema, marked by destruction of the alveolar region of the lungs, and chronic bronchitis, or long-term inflammation of the bronchial tubes. These studies are discussed below. There are no recent animal toxicological studies examining long-term exposure to $PM_{2.5}$ and COPD.

Recent large cohort studies examined the association between long-term $PM_{2.5}$ and COPD development. In a study of COPD incidence in the U.K., a dispersion model was used to assign annual-average $PM_{2.5}$ exposure to nearest postcode centroid for each patient (Atkinson et al., 2015). The authors reported that $PM_{2.5}$ was associated with higher odds of first COPD hospitalization (OR [95% CI]: 1.14 [0.96, 1.36]), but not for COPD diagnosis from a general practitioner (0.98 [0.84, 1.16]). Hospital admissions records may represent more severe cases of COPD, which may explain the difference in effect

estimates. The COPD hospitalization results persisted in two-pollutant models with SO_2, NO_2 and O_3 ($r < 0.5$ for all pollutants). Similarly, 5-year average $PM_{2.5}$ was associated with an increase, with wide confidence intervals, in the risk of hospitalization due to COPD (RR [95% CI]: 1.06 [0.93, 1.20]) in a large population-based cohort in metropolitan Vancouver (Gan et al., 2013). The study was limited to participants who had no previous record of COPD diagnosis, but hospitalization records were analyzed only for a few years prior. Thus, the hospitalization could reflect exacerbation of a previously diagnosed disease, rather than COPD onset. In a large cohort study of chronic disease prevalence in women living in Ontario, Canada, To et al. (2015) assigned $PM_{2.5}$ exposure at a postal code level using satellite-based AOD observation data. The authors reported that the incidence and prevalence of COPD were associated with 8-year average $PM_{2.5}$ concentrations. Contrasting evidence was observed in an ESCAPE Project pooled analysis of four European cohorts (Schikowski et al., 2014). COPD was defined using prebronchodilator FEV_1/FVC below the lower limit of normal (LLN) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition (FEV_1/FVC <0.70). Annual $PM_{2.5}$ concentrations, estimated by LUR, were not associated with incidence (OR [95% CI]: 1.06 [0.73, 1.53]) or prevalence (OR [95% CI]: 0.95 [0.47, 1.9]) of COPD defined by LLN. Similar estimates were obtained using the GOLD definition of COPD.

A limited number of studies examined specific forms of COPD, including emphysema and chronic bronchitis. As discussed in the 2009 PM ISA (U.S. EPA, 2009), McConnell et al. (2003) reported associations between annual and 4-year average $PM_{2.5}$ and bronchitic symptoms in a prospective study of children in 12 CHS communities. A recent pooled analysis of five European cohorts also examined chronic bronchitis in relation to $PM_{2.5}$ (Cai et al., 2014). Annual average $PM_{2.5}$ concentrations were not associated with chronic bronchitis in the overall population (OR [95% CI]: 0.90 [0.74, 1.09]), but was associated with chronic bronchitis in a subanalysis of nonsmokers (OR [95% CI]: 1.28 [0.95, 1.72]). A U.S. cross-sectional study using data from the National Health Interview Survey (NHIS) also observed an association between $PM_{2.5}$ concentrations in the past year and the odds of chronic bronchitis (OR [95% CI]: 1.08 [0.94, 1.24]) (Nachman and Parker, 2012). The association between emphysema and exposure to $PM_{2.5}$ was examined cross-sectionally in the MESA study (Adar et al., 2015). PM concentrations 1 year prior to baseline exam and 20-year average exposures were estimated. Percent emphysema, determined from CT scans, was positively associated with both 1-year average and 20-year average $PM_{2.5}$. However, these results were driven by lower mean percent emphysema in one city (St. Paul) with the lowest $PM_{2.5}$ concentrations, and the associations were no longer positive after adjustment for study site, or in analyses excluding St. Paul.

Recent studies provide some evidence that long-term $PM_{2.5}$ exposure may be associated with development of COPD in adults, but uncertainties remain. Notably, studies of COPD hospitalization may reflect exacerbation of previously diagnosed disease rather than disease onset. Additionally, hospitalizations may represent severe cases of COPD and may not account for the potential effect of short-term exposures leading to these acute events. There is also a lack of available studies that examine potential copollutant confounding. However, one study observed that $PM_{2.5}$ was associated with first-time

COPD hospitalization independent of gaseous pollutants (Atkinson et al., 2015). Overall, a limited number of studies also provide evidence of an association between long-term exposure to $PM_{2.5}$ and chronic bronchitis, a specific form of COPD.

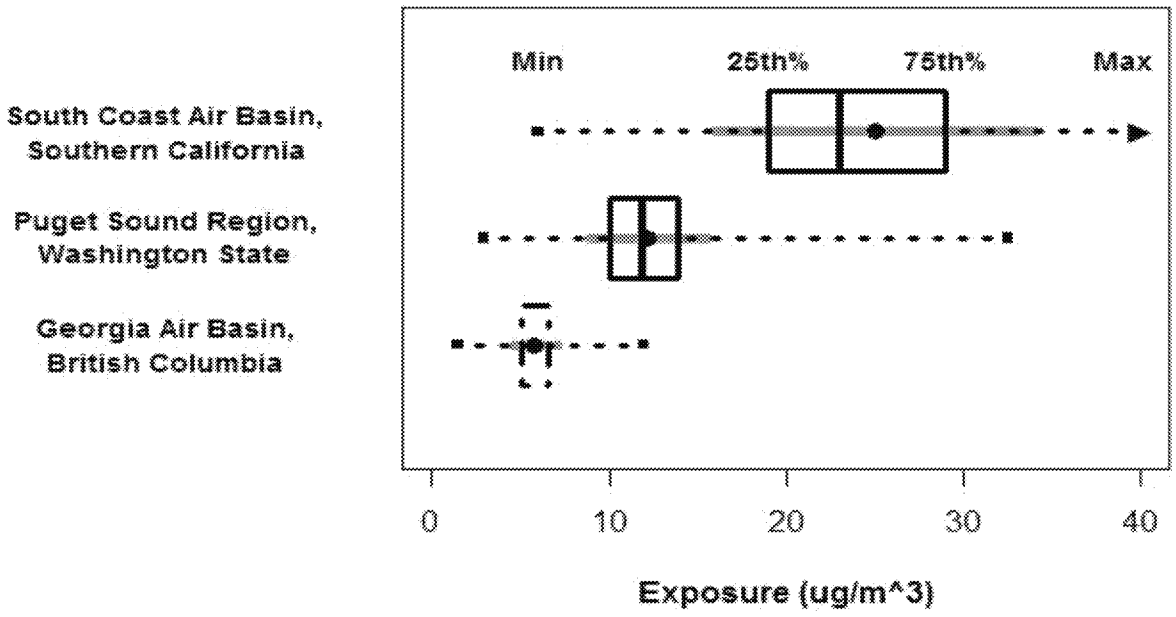
5.2.6 Respiratory Infection

In the 2009 PM ISA (U.S. EPA, 2009), results from epidemiologic studies indicated an association between PM and respiratory infection. However, this association was largely evident in studies of short-term PM exposure, as only one study examined the relationship between long-term exposure to $PM_{2.5}$ and respiratory infection. Several animal toxicological studies examined the effects of long-term exposure to DE on host defense. While evidence for altered host defense was found, these studies did not distinguish between effects due to gases or particles in the DE mixture. Recent epidemiologic studies in North America and Europe have examined the associations between long-term exposure to $PM_{2.5}$ and infant bronchiolitis, pneumonia, croup, and otitis media. There are no recent animal toxicological studies of long-term $PM_{2.5}$ exposure and host defense.

The association between infant bronchiolitis and long-term $PM_{2.5}$ exposure was examined in three large cohorts (Karr et al., 2009b; Karr et al., 2009a; Karr et al., 2007). A prominent respiratory infection in infancy, bronchiolitis is primarily caused by the respiratory syncytial virus (RSV), and results in inflammation of the bronchioles. As discussed in the 2009 PM ISA (U.S. EPA, 2009), Karr et al. (2009b) examined infant bronchiolitis hospitalization in a birth registry cohort in the Puget Sound region of Washington. Two similar studies, which were not reviewed in the 2009 PM ISA, also examined infant bronchiolitis in the Georgia Air Basin of British Columbia (Karr et al., 2009a) and the South Coast Air Basin of California (Karr et al., 2007). Each nested case-control study examined cumulative lifetime exposure to $PM_{2.5}$ in relation to bronchiolitis incidence in the first year of life. The results were inconsistent across studies.

Karr et al. (2009b) assigned lifetime average $PM_{2.5}$ from the closest fixed-site monitor within 20 km of subjects' residential postal code. The authors reported that $PM_{2.5}$ concentrations were associated with RSV bronchiolitis, but not all bronchiolitis, which includes bronchiolitis due to other infectious agents. However, in a model examining effect modification, Karr et al. (2009b) reported an association with all bronchiolitis for infants living within 5 km of a fixed-site monitor. The restricted analysis may have reduced exposure measurement error, as infants spend most of their time in or near their homes (Wiley et al., 1991). Karr et al. (2007) did not exclude maternal-infant pairs based on distance to monitor but reported that 90% of study participants lived within 17.7 km of a monitor. The authors observed a 4% increase in the odds of bronchiolitis hospitalization in the first year of life in relation to cumulative lifetime $PM_{2.5}$ exposure (95% CI: 2, 7%). The association with $PM_{2.5}$ was robust to the inclusion of O_3 in a copollutant model (4% [95% CI: 1.03 to 1.15]; $r = -0.24$). In contrast to evidence observed in Washington (Karr et al., 2009b) and California (Karr et al., 2007), Karr et al. (2009a) reported null

associations between lifetime $PM_{2.5}$ exposure and infant bronchiolitis in British Columbia. The analysis included infants living within 10 km of a monitor and modeled exposure concentrations using an LUR model to produce similar results. A comparison of the $PM_{2.5}$ distributions across the three studies shows that mean concentration and variance are smallest in British Columbia (Figure 5-33). The narrow exposure range, resulting in limited variability in $PM_{2.5}$ concentrations, may have contributed to the lack of an observed association.



Note: Large dots represent means; bold vertical lines represent medians. Red lines represent ± one standard deviation. For British Columbia, 25th and 75th percentiles were not reported, and so the IQR was assumed to center around the mean value. The maximum value for Southern California was 111.0 μg/m^3. The IQR's were 10, 3.8, and 1.5 μg/m^3, respectively.

Figure 5-33 Exposure measurements from South Coast Air Basin (Karr et al., 2007), Puget Sound Region, WA (Karr et al., 2007), and Georgia Air Basin, British Columbia (Karr et al., 2009b).

A limited number of studies evaluated other respiratory infection endpoints in infants or adults. MacIntyre et al. (2014b) examined parental reported pneumonia, otitis media, and croup in an ESCAPE Project pooled analysis of 10 European cohorts. $PM_{2.5}$ estimated outside birth residence was associated with an imprecise increase in odds of pneumonia in the first 36 months of life across all cohorts (OR [95% CI]: 2.58 [0.91, 7.27]). The association with $PM_{2.5}$ was attenuated, but still positive, in a two-pollutant model adjusting for NO_2 (1.91 [0.56, 6.57]; $r = 0.42–0.8$). A sensitivity analysis looking at alternative outcome windows showed the strongest association between long-term $PM_{2.5}$ and pneumonia diagnosed in the first year of life. Associations were null or negative for croup and otitis media. In a

case-control study in Ontario, Canada, Neupane et al. (2010) assessed the risk of hospitalization for community-acquired pneumonia in adults 65 years of age or older in relation to long-term exposure to $PM_{2.5}$. A notable strength of this study was the use of radiologically confirmed pneumonia to reduce potential outcome misclassification. The authors assigned exposure at the residential level using two deterministic interpolation methods, bicubic splines and inverse distance weighting, to estimate $PM_{2.5}$ concentrations at locations not coinciding with four air-quality monitors. Risk of hospitalization for pneumonia was associated with annual average $PM_{2.5}$ concentration, as estimated by both bicubic splines (OR [95% CI]: 1.6 [0.99, 2.63]) and inverse-distance weighting (3.7 [1.3, 10.1]). However, given the acute nature of the examined outcome, some uncertainty remains regarding potential confounding due to short-term $PM_{2.5}$ exposure.

In summary, recent epidemiologic studies do not indicate a clear relationship between long-term $PM_{2.5}$ exposures and respiratory infection in infants or adults. While the limited number of studies reviewed generally reported associations between $PM_{2.5}$ and at least some of the examined respiratory infection outcomes, there was limited overlap in endpoints across studies. Where the same endpoint was examined across multiple studies, large birth cohort studies found some evidence of an association between $PM_{2.5}$ and infant bronchiolitis (Karr et al., 2009b; Karr et al., 2007), but the results were not entirely consistent (Karr et al., 2009a).

5.2.7 Severity of Respiratory Disease

The 2009 PM ISA (U.S. EPA, 2009) reported evidence of an association between long-term $PM_{2.5}$ concentrations and increased severity of respiratory disease in two cohort studies. In one of these, an association between long-term $PM_{2.5}$ concentrations and increased disease severity was indicated by higher odds of bronchitic symptoms in children with asthma (McConnell et al., 2003). Stages of asthma can range in severity from mild, moderate, moderate-persistent, to severe (NHLBI NAEPP, 2007). In a second cohort study reported in the 2009 PM ISA (U.S. EPA, 2009), there was evidence for higher odds of exacerbation in persons with cystic fibrosis (CF). Goss et al. (2004) observed that long-term $PM_{2.5}$ exposure was associated with increased odds of two or more CF exacerbations. CF exacerbations were defined as a CF-related pulmonary condition requiring admission to the hospital or use of home intravenous antibiotics. Particle deposition is increased in CF and particle distribution in the lungs is enhanced in poorly ventilated tracheobronchial regions in CF patients (Brown et al., 2001). Such focal deposition may partially explain the reported association of PM and CF exacerbation. No recent studies examined CF exacerbations in relation to long-term $PM_{2.5}$ concentrations. The 2009 PM ISA also evaluated an animal toxicological study that reported exacerbation of an asthma-like phenotype following long-term DE exposure. However, this study did not distinguish between effects due to gases or particles in the mixture. In addition, animal toxicological evidence for COPD exacerbation following long-term exposure to urban air exposure was reported, however there was no measurement of $PM_{2.5}$ concentrations.

A limited number of recent epidemiologic studies show an association between long-term exposure to $PM_{2.5}$ and severity demonstrated by increased risk of asthma hospitalizations and ED visits in children. A recent study also provides evidence of a similar association in adults. However, potential confounding by short-term exposures remains an uncertainty in ascertaining the independent effect of long-term $PM_{2.5}$ exposure. One recent animal toxicological study evaluated the exacerbation of asthma in an animal model of allergic airway disease.

5.2.7.1 Epidemiologic Studies

Exacerbation of asthma symptoms is an indicator of severity, with more severe symptoms potentially resulting in hospitalization. Recent studies have evaluated the relationship between long-term exposure to $PM_{2.5}$ and asthma-related hospitalizations and ED visits in children. In a cross-sectional analysis using data from the California Health Interview Survey (CHIS), Wilhelm et al. (2008) assessed asthma hospitalization and emergency room visits in children 0 to 17 years old. Annual average $PM_{2.5}$ concentrations in Los Angeles and San Diego counties, measured by the nearest monitor within a 5-mile range, were not strongly associated with increased odds of asthma-related hospitalizations or emergency room visits (OR: 1.04 [95% CI: 0.68, 1.58]). However, there was an association in a copollutant model controlling for O_3 (OR: 1.9 [95% CI: 0.99, 3.7]). Meanwhile, a population-based cohort study of children in Quebec, Canada, the design of which is described in more detail in Tétreault et al. (2016a) and Section 5.2.3.1, also examined exacerbation of asthma in children (Tétreault et al., 2016b). The authors reported increases in hospital admissions and ED visits in relation to $PM_{2.5}$ concentrations measured outside birth residence (HR: 1.15 [95% CI: 1.14 to 1.15]) and using a time-varying model (HR: 1.07 [95% CI: 1.05 to 1.09]). $PM_{2.5}$ concentrations were estimated over a 10 × 10 km grid using satellite-based AOD observation data downscaled by the GEOS-Chem CTM. While these studies provide some evidence of an association between long-term exposure to $PM_{2.5}$ and asthma severity, neither study controlled for short-term exposures. Given the acute nature of the health endpoint, the observed effect could be partially or fully attributable to short-term increases in air pollution on the days prior to admission. Increases in asthma symptoms were also associated with long-term $PM_{2.5}$ concentrations in a cross-sectional study of adults (Balmes et al., 2014). Although asthma symptoms were self-reported using a nonvalidated ordinal questionnaire, responses are unlikely to be differentially misclassified according to exposure. Overall, recent studies examine asthma exacerbation in children and adults and provide additional evidence of a $PM_{2.5}$ effect on asthma severity. However, given the acute nature of the examined outcomes, some uncertainty remains regarding potential confounding due to short-term $PM_{2.5}$ exposure.

5.2.7.2 Animal Toxicological Study

Recently, a study evaluating the effects of $PM_{2.5}$ on severity of disease has become available. In Farraj et al. (2010), the effects of long-term DEP exposure were studied in an allergic mouse model.

BALB/c mice, which had been sensitized with OVA, were exposed to DEP for 4 weeks, with OVA challenges occurring at 2 and 4 weeks. DEP exposure had no effect on the many OVA-induced changes in BALF cells, cytokines, and injury markers (LDH, albumin, protein), except for a decrease in IL-4 ($p < 0.05$). This may be due to the analysis occurring 5 days after the last DEP exposure. Typically, acute inflammatory responses are measured at 24–48 hours after exposure to PM. Furthermore, Farraj et al. (2010) found that DEP exposure had no effect on airway responsiveness, as assessed by methacholine-induced changes in lung resistance, in the allergic mice. Additional study details for this study are found in Table 5-24.

Table 5-24 Study-specific details from an animal toxicological study of long-term $PM_{2.5}$ exposure and severity of an asthma-like phenotype.

Study/Study Population	Pollutant	Exposure	Endpoints
Farraj et al. (2010) Species: Mouse Sex: Male Strain: BALB/c Age/Weight: 6 weeks	Diesel exhaust particles (DEP) NIST SRM 29 + 5 Particle size: 1.2 µm MMAD Control: Saline aerosol	Route: Nose only inhalation Dose/Concentration: 2.0 mg/m³ Duration: 1 time per week for 4 weeks Time to analysis: 5 d from last DEP Coexposure: Sham sensitization and saline aerosols. Diesel combustion gases not defined.	Lung injury • BALF LDH, albumin, and protein BALF cytokines Lung function

BALF = bronchoalveolar lavage fluid; LDH = lactate dehydrogenase; MMAD = mass median aerodynamic diameter; NIST SRM = National Institute of Standards and Technology Standard Reference Material.

5.2.8 Subclinical Effects in Healthy Populations

Animal toxicological studies provide evidence for subclinical effects potentially underlying the development of respiratory disease in healthy populations. The 2009 PM ISA (U.S. EPA, 2009) reported several studies that evaluated the effects of long-term exposure to $PM_{2.5}$ on subclinical effects in healthy populations. These studies provided evidence of pulmonary injury, inflammation, oxidative stress, and morphological alterations following long-term exposure to DE, GE, and woodsmoke. While most studies made no effort to distinguish between effects due to gases or particles in the mixture, one study examined the effects of particle filtration. Injury and inflammatory responses to DE were diminished as a result of particle filtration, indicating that PM played a role in the responses. Recent animal toxicological studies examined subclinical effects related to an asthma-like phenotype as discussed above (see

Section 5.2.3.3.2 and Section 5.2.7). Other respiratory-related subclinical effects, including oxidative stress, inflammation, and altered morphology have been investigated in studies of long-term $PM_{2.5}$ exposure. These results are discussed below, with additional study details found in Table 5-25.

Pulmonary Oxidative Stress

The 2009 PM ISA (U.S. EPA, 2009) evaluated several studies that examined pulmonary oxidative stress following long-term exposure to DE. These studies did not distinguish between effects due to gases or particles in the mixture. Recently, Kampfrath et al. (2011) investigated the effects of a 20-week exposure to $PM_{2.5}$ CAPs in Columbus, OH on oxidized phospholipids in the lung. Responses were compared in wild type and Toll-like receptor 4 (TLR4) deficient BALB/c mice. Increased levels of two oxidized forms of 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine (PAPC), the most common phospholipid in BALF, were observed in wild type mice exposed to $PM_{2.5}$ CAPs. Statistical analysis of these results was not presented. In a follow up study, Deiuliis et al. (2012) demonstrated the presence of oxidized PAPC in BALF in C57BL/6 mice exposed for 28 weeks to $PM_{2.5}$ CAPs in Columbus, OH ($p = 0.001$), thus confirming the results of (Kampfrath et al., 2011). Since oxidized lipids play a role in activating T cells, inflammatory T cells were also examined (see below). Aztatzi-Aguilar et al. (2015) found increased lung tissue heme oxygenase-1 activity in Sprague Dawley rats following 8-weeks exposure $PM_{2.5}$ CAPs in Mexico City ($p < 0.05$), while no changes in γ-glutamyl cysteine ligase catalytic subunit, another index of oxidative stress, were observed.

Table 5-25 Study-specific details from animal toxicological studies of long-term $PM_{2.5}$ exposure and subclinical effects.

Study/Study Population	Pollutant	Exposure	Endpoints
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley	$PM_{2.5}$ CAPs Mexico City Particle size: $PM_{2.5}$ Control: Filtered air	Route: Inhalation Dose/Concentration: $PM_{2.5}$ 178 µg/m^3 Duration: Acute 5 h/day, 3 days Subchronic 5 h/day, 4 days/week, 8 weeks Time to Analysis: 24 h	Gene and protein expression • IL-6 • Kallikrein-kinin system • RAS • Heme oxygenase-1
Deiuliis et al. (2012) Species: Mouse Sex: Male Strain: C57BL/6 (wild type) • CXCR3 knockout • Foxp3-GFP knockout Age/Weight: 12 weeks	$PM_{2.5}$ CAPs Columbus, OH Particle size: ≤$PM_{2.5}$ Control: HEPA-filtered air	Route: Whole-body inhalation Dose/Concentration: 115.5 µg/m^3 Duration: 6 h/day, 5 days/week, 24–28 weeks Time to analysis: 1 h	Histopathology—lung Oxidative stress: • oxidized PAPC in BALF T cell subsets • $CD3^+$ lymphocytes—T regs Gene expression-1L-17α, and CXCR3 gene expression in $CD4^+$ T cells from lung
Guo et al. (2017) Species: Rat Strain: Sprague Dawley Sex: Female Age/Weight: 4–5 weeks	Ambient particles (Shanghai, China), liquid aerosol generator Particle size: $PM_{2.5}$ Control: Saline aerosol	Route: Whole-body inhalation Dose/Concentration: 200, 1,000, and 3,000 µg/m^3 Duration: 3 h/day for 30 days	Nasal mucosa- • Malondialdehyde • SOD • ATPases • Mitochondrial mRNA and protein • Histological and ultrastructural analysis • Serum cytokines
Kampfrath et al. (2011) Species: Mouse Sex: Male Strain: BALB/c (wild type) and TLR4 knockout Age/Weight: 6 weeks	$PM_{2.5}$ CAPs Columbus, OH Particle size: ≤$PM_{2.5}$ Control: HEPA-filtered air	Route: Whole-body inhalation Dose/Concentration: 92.4 µg/m^3 Duration: 6 h/day, 5 days/week, 20 weeks	Oxidative stress: Oxidized PAPC in BALF

Table 5-25 (Continued): Study specific details from animal toxicological studies of long term $PM_{2.5}$ exposure and subclinical effects.

Study/Study Population	Pollutant	Exposure	Endpoints
Kim et al. (2016a) Species: Mouse Strain: BALB/c Sex: Female Age/Weight: 5–6 weeks	DEP nebulized Particle size: Mean diameter 0.4 μm before nebulization and 1–5 μm after nebulization Control: Saline aerosol	Dose/Concentration: 0.1 and 3 mg/m^3 DEP or saline (only results from 0.1 mg/m^3 reported here) Duration: 1 h/day, 5 days/week for 4, 8, and 12 weeks Time to analysis: 1 day after last exposure	BALF cells BALF cytokines Histochemistry • Masson trichome staining of lung
Ramanathan et al. (2017) Species: Mouse Strain: C57BL/6 Sex: Male Age/Weight: 8 weeks	$PM_{2.5}$ CAPs Baltimore, MD Particle size: $PM_{2.5}$ Control: Filtered air	Dose/concentration: 60.92 ± 21.31 μg/m^3 Controls: 8.09 ± 2.61 μg/m^3 Duration: 6 h/day, 5 days/week, 16 weeks	Nasal histopathology Nasal airway lavage: Inflammatory cells, cytokines, albumin
Tyler et al. (2016) Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6–8 weeks	DEP, resuspended Particle size: 1.5–3.0 μm ± 1.3–1.6 μm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 315.3 ± 50.7 μg/m^3 Duration: 6 h/days for 30 days	BALF cells and cytokines Particle uptake in bronchial macrophages

ApoE = apolipoprotein E; ATPase = adenosine triphosphatase; BALF = bronchoalveolar lavage fluid; CD = cluster of differentiation; CXCR3 = chemokine receptor CXCR3; DEP = diesel exhaust particle; Foxp3 = forkhead box P3; IL-6 = interleukin-6; IL-17 α = interleukin-17 α; PAPC = 1-palmitoyl-2-arachidonoyl-sn-phosphatidylcholine; RAS = renin-angiotensin system; SOD = superoxide dismutase, T-regs = regulatory T lymphocytes; TLR4 = toll-like receptor 4.

1

Pulmonary Inflammation

2 The 2009 PM ISA (U.S. EPA, 2009) reported several studies evaluating pulmonary inflammation
3 following long-term exposure to DE and woodsmoke. These studies did not distinguish between effects
4 due to gases or particles in the mixture. Recently, Deiuliis et al. (2012) exposed wild type C57BL/6 mice
5 and mice deficient in T cell chemokine receptor 3 (CXCR3) for 28 weeks to $PM_{2.5}$ CAPs in Columbus,
6 OH. $PM_{2.5}$ CAPs exposure resulted in increased numbers of CD11c+, but not CD11b+, macrophages
7 ($p < 0.0002$) in the lungs of wild type mice, as assessed by flow cytometry. CXCR3 deficiency decreased
8 basal numbers of these macrophage subtypes and responses to $PM_{2.5}$ CAPs exposure. In wild type mice,
9 $PM_{2.5}$ CAPs exposure resulted in increased numbers of T cell subsets, including $CD3^+$ ($p = 0.005$), $CD4^+$
10 ($p = 0.007$), and CD8+ lymphocytes ($p = 0.04$), Basal levels of these subsets and responses to $PM_{2.5}$ CAPs
11 exposure were attenuated in CXCR3-deficient mice. A similar pattern of response was observed for
12 activated CD44 + CD62L - CD4 + T cells ($p = 0.01$). However, in the case of central memory
13 CD44 + CD62L - CCR7 + T cells, $PM_{2.5}$ CAPs exposure induced increases in both wild-type ($p = 0.01$)
14 and CXCR4-deficient mice ($p = 0.04$). Expression of CXCR3 on $CD4^+$($p = 0.005$), but not $CD8^+$, T cells
15 was increased by $PM_{2.5}$ CAPs. Gene expression was also evaluated in isolated lung $CD4^+$ T cell.

Long-term $PM_{2.5}$ CAPs exposure increased expression of CXCR3 and, IL-17α, but not CCR3, CCR4, and IL-4. These results show that long-term exposure to $PM_{2.5}$ CAPs induced T cell infiltration and increased activation of effector T cells in the lungs and suggests a Th1 rather than a Th2 response. The role of CXCR3 in mediating the effects of $PM_{2.5}$ CAPs is unclear since its deficiency had effects on both basal and PM-stimulated inflammation. Results of this study indicate that activation of macrophages by oxidized phospholipids (see above) may lead to the release of cytokines which recruit and activate T cells as part of a proinflammatory Th1 response.

Kim et al. (2016a) exposed BALB/c mice to nebulized DEP for 4, 8, and 12 weeks. DEP exposure resulted in increased numbers of BALF lymphocytes at 4 and 12 weeks ($p < 0.05$). Numbers of other inflammatory cells and total cells in BALF were not altered. However, increased levels of cytokines IFN-γ, IL-6, VEGF, and TGF-β were observed in BALF at 12 weeks ($p < 0.05$). In contrast, two other studies found no evidence of inflammation following long-term $PM_{2.5}$ exposure. No increase in BALF inflammatory cells or cytokines or particle uptake into bronchial macrophages was observed in C57BL/7 mice exposed to resuspended DEP for 30 days (Tyler et al., 2016). However, inflammatory effects were observed in the hippocampus (Section 8.1.3). Aztatzi-Aguilar et al. (2015) exposed Sprague Dawley rats for 8 weeks to $PM_{2.5}$ CAPs in Mexico City and found decreased protein expression of IL-6 in lung tissue ($p < 0.05$). However, long-term $PM_{2.5}$ CAPs exposure also had several effects on the RAS in the lung ($p < 0.05$). This included induced lung expression of the angiotensin 1 receptor gene, and increased angiotensin 1 receptor protein levels. Protein levels and mRNA of angiotensin converting enzyme were not impacted. Components of the RAS play an important role in the pulmonary circulation.

Morphological Effects

In a long-term exposure study involving DEP, Kim et al. (2016a) found increased collagen deposition, as assessed by Masson trichrome staining, at 4, 8, and 12 weeks ($p < 0.05$) (see Section 5.2.3.3.2). Increased and disordered collagen deposition underlies lung fibrosis, which is mediated in part by the cytokine TGF-β, whose levels were increased as a result of DEP exposure in this study ($p < 0.05$).

Recent studies also examine effects on nasal mucosa (Guo et al., 2017) (Ramanathan et al., 2017). (Guo et al., 2017) evaluated nasal injury and oxidative stress in Sprague Dawley rats following 30-day inhalation of two concentrations of resuspended $PM_{2.5}$ from Shanghai, China. Long-term Exposure to $PM_{2.5}$ resulted in increased malondialdehyde levels in nasal mucosa ($p < 0.05$). Morphological alterations were observed, including nasal epithelial necrosis, disarray of cilia, vascular congestion, and edema. At the ultrastructural level, mitochondrial alterations were observed, including swelling, cristae disorder, and vacuolization. Activities of several enzymes (superoxide dismutase, sodium potassium ATPase, calcium ATPase) in nasal mucosa were decreased by exposure ($p < 0.01$). Gene expression and protein levels of OPA1 and Mnf1, which are involved in mitochondrial fusion and fission, were increased by long-term exposure to both concentrations of $PM_{2.5}$ ($p < 0.01$). Ramanathan et al. (2017) examined the effects of a

16-week exposure to $PM_{2.5}$ CAPs in Baltimore, MD on the sinonasal barrier of C57BL/6 mice. Numbers of macrophages, neutrophils, and eosinophils were increased in NALF ($p < 0.05$). Levels of proinflammatory cytokines were also increased in NALF, including IL-1β, IL-13, and eotaxin-1. Immunostaining of sinonasal mucosa revealed increased staining for myeloperoxidase and eosinophil major basic protein positive cells ($p < 0.05$). Evidence for sinonasal epithelial cell barrier dysfunction was provided by decreased expression of tight junction and adherens junction proteins claudin-1 and E-cadherin and by increased levels of serum albumin in NALF ($p < 0.05$). Furthermore, morphometric analysis of the septal subepithelial thickness showed an increase as a result of long-term exposure to $PM_{2.5}$ ($p < 0.001$).

Summary of Subclinical Effects in Healthy Populations

Recent studies and one older study provide evidence for several subclinical effects potentially underlying the development of respiratory disease following long-term $PM_{2.5}$ exposure in healthy animal models. These include pulmonary injury, oxidative stress, inflammation and altered morphology. In particular, increases in tissue and BALF expression of antioxidant genes and proteins and increases in BALF levels of oxidized phospholipids were found. Upregulation of cytokines in the lungs and infiltration of inflammatory cells, including lymphocytes, monocytes, and specific T-cells subtypes consistent with a Th1 proinflammatory response, were also observed. In addition, long-term $PM_{2.5}$ exposure resulted in increased collagen deposition, an early step in the development of lung fibrosis, and upregulation of the RAS. While the above-mentioned studies focused on the lower airways, changes to the upper airways were also demonstrated. Two studies found evidence of oxidative stress, injury, inflammation, and morphologic changes in nasal mucosa resulting from long-term exposure to $PM_{2.5}$.

5.2.9 Subclinical Effects in Populations with Cardiovascular Disease

Animal toxicological studies provide evidence for subclinical effects potentially underlying the development of respiratory disease in populations with cardiovascular disease. The 2009 PM ISA (U.S. EPA, 2009) reported several studies that evaluated the effects of long-term exposure to $PM_{2.5}$ in animal models of cardiovascular disease, mainly focusing on pulmonary inflammation. In ApoE and LDL knock-out mice, exposure for 1–5 months to $PM_{2.5}$ CAPs resulted in upregulation of gene expression in lung tissue, although no increases in BALF inflammatory cells were found. Inflammation and altered morphology were observed following long-term exposure to DE in spontaneously hypertensive (SH) rats. However, there was no attempt to distinguish between effects due to gases or particles in the DE mixture.

Recent studies examined pulmonary oxidative stress and inflammation. Evidence for pulmonary inflammation was found in SH rats exposed to $PM_{2.5}$ CAPs in Columbus, OH for 15 weeks (Ying et al., 2015). Expression of TNFα and IL-6 mRNA in lung tissue was increased at 15 weeks ($p < 0.05$) and remained elevated 5 weeks following the end of exposure. Xu et al. (2012) exposed ApoE knockout mice

to $PM_{2.5}$ CAPs in Tuxedo, NY for 3 months. Monocytic infiltration into the lung was observed, as evidenced by increased numbers of $F4/F80^+$ macrophage ($p < 0.001$). Wan et al. (2014) conducted a 2-month long field study of ApoE knockout mice exposed to ambient air in Beijing and fed a Western diet. Urban air PM mainly consisted of $PM_{2.5}$, but it also contained some PM_{10}; other ambient pollutants were also present. Control mice were exposed to filtered ambient air, which contained greatly reduced concentrations of $PM_{2.5}$. Long-term exposure to Beijing urban air increased BALF levels of oxidized LDL and MDA, decreased BALF SOD and GSHPx activity and increased BALF levels of IL-6 and TNF-a protein ($p < 0.05$). In contrast, Tyler et al. (2016) exposed ApoE knockout mice to resuspended DEP for 30 days and found no increase in inflammatory cells or cytokines in the BALF, although particle uptake into bronchial macrophages was increased ($p < 0.001$). Effects were also seen in the hippocampus (Section 8.2.3). Overall, evidence for inflammation was found in lung tissue following long-term exposure to $PM_{2.5}$ CAPs, but not in BALF following long-term exposure to DEP. Interpretation of effects due to long-term urban air exposure is complicated by the presence of $PM_{10-2.5}$. Additional study details are found in Table 5-26.

Table 5-26 Study-specific details from animal toxicological studies of long-term $PM_{2.5}$ exposure and subclinical effects in populations with cardiovascular disease.

Study/Study Population	Pollutant	Exposure	Endpoints
Tyler et al. (2016) Species: Mouse Strain: ApoE knockout Age/Weight: 6–8 weeks	DEP, resuspended Particle size: 1.5–3.0 µm ± 1.3–1.6 µm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 315.3 ± 50.7 µg/m^3 Duration: 6 h/day for 30 days	BALF cells and cytokines Particle uptake in bronchial macrophages
Wan et al. (2014) Species: Mouse Strain: Apo E knockout C57BL/6) Sex: Male Age/Weight: 9 weeks	Beijing PM Particle sizes: $PM_{2.5}$ + PM_{10} Control: HEPA-filtered ambient air	Route: Ambient Beijing air Dose/concentration: $PM_{2.5}$ 63.1 µg/m^3 $PM_{10-2.5}$ 37.2 µg/m^3 (estimated as the difference of PM_{10} and $PM_{2.5}$ concentration measurements made with one continuous monitor) Duration of exposure: 24 h/day, 7 days/week for 2 mo Coexposure Western Diet	BALF Cytokines- IL-6 and TNF-α Oxidative stress markers—Ox LDL, malondialdehyde, SOD and GSHPx
Xu et al. (2012) Species: Mouse Strain: Apo E knockout Sex: Male Age/Weight: 8 weeks	$PM_{2.5}$ CAPs Tuxedo NY Particle sizes: $PM_{2.5}$ Control: Filtered air	Route: Whole-body inhalation Dose/concentration: $PM_{2.5}$ CAPs 70 µg/m^3 Duration of exposure: 6 h/day, 5 days/week for 3 mo	Histopathology—lung
Ying et al. (2015) Species: Rat Strain: SHR Sex: Male Age/Weight: 5 weeks	$PM_{2.5}$ CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 128.3 ± 60.4 µg/m^3 Duration: 6 h/day, 5 days/week for 15 weeks Time to analysis: Immediately or 5 weeks later	Gene expression—inflammatory markers in lung

ApoE = apolipoprotein E; BALF = bronchoalveolar lavage fluid; DEP = diesel exhaust particle; GSHPX = glutathione peroxidase; HEPA = high efficiency particulate absorber; IL-6 = interleukin-6; OxLDL = oxidized low density lipoprotein; SHR = spontaneously hypertensive rat; SOD = superoxide dismutase; TNF α = tumor necrosis factor α.

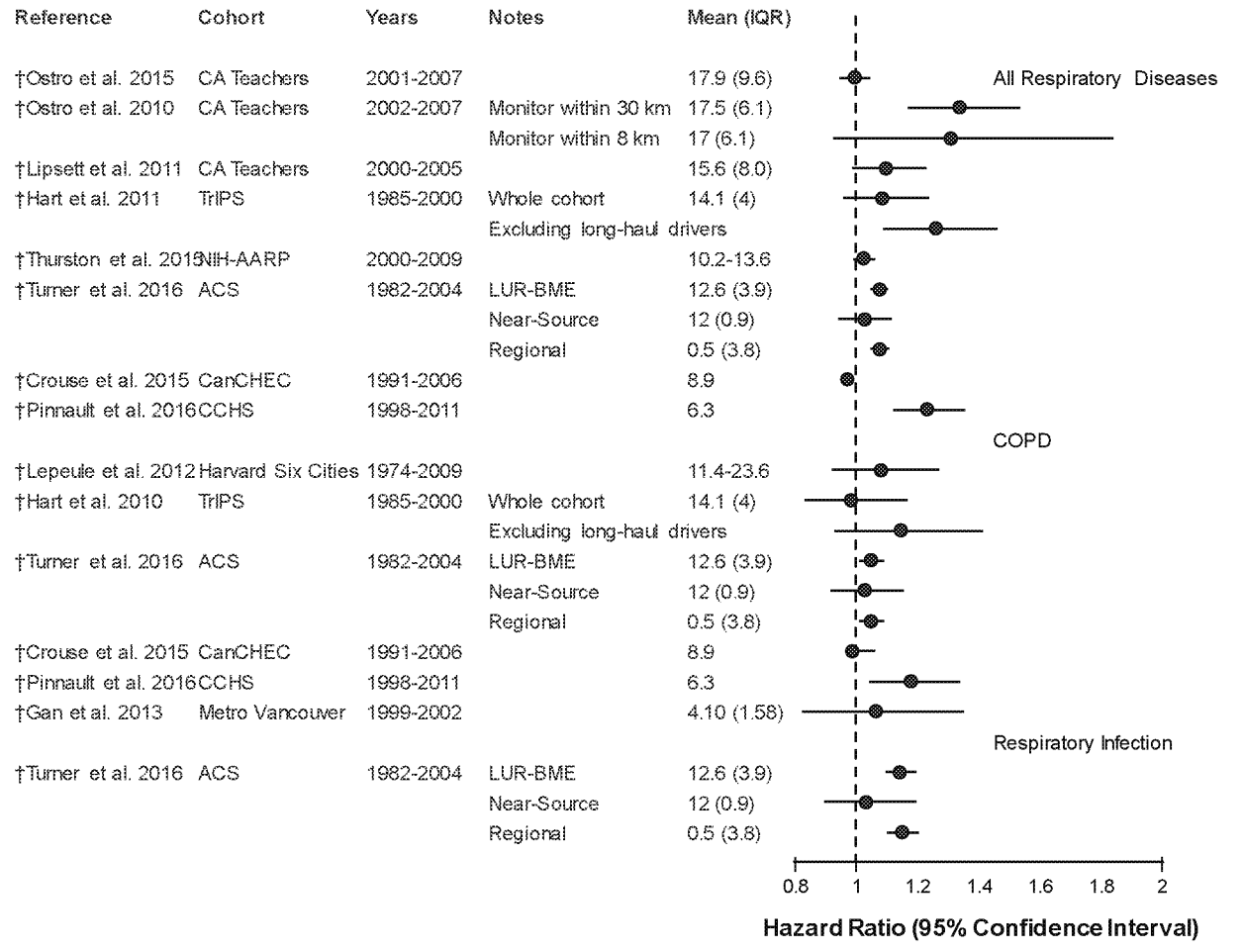
5.2.10 Respiratory Mortality

Studies that examine the association between long-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as respiratory mortality, provide additional evidence for $PM_{2.5}$-related respiratory effects, specifically whether there is evidence of an overall continuum of effects. Evidence from studies of long-term $PM_{2.5}$ exposure and mortality are presented in detail in CHAPTER 11.

Evidence from studies investigating respiratory mortality provided limited and inconsistent evidence for a respiratory effect related to long-term $PM_{2.5}$ exposure in the 2009 PM ISA (U.S. EPA, 2009) and are summarized here to inform the effect of long-term $PM_{2.5}$ exposure on the continuum of respiratory health effects. The 2009 PM ISA (U.S. EPA, 2009) included evidence from two large, multicity U.S. studies: the American Cancer Society (ACS) cohort (Pope III et al., 2004) and the Harvard six cities cohort (Laden et al., 2006). Recent updates to these studies, as well as results from recent cohort studies, contribute to the body of evidence for this relationship (Figure 5-34).

Several recent analyses further evaluated the associations of long-term $PM_{2.5}$ exposures with risk of respiratory mortality based on the original ACS study (Pope et al., 1995), adding details about deaths due to respiratory disease (including COPD), and extending the follow-up period for the ACS to 22 years (1982−2004). In particular, Pope et al. (2014) and Turner et al. (2016) used the extended follow-up period of the ACS to examine the associations between long-term $PM_{2.5}$ exposure and respiratory disease and COPD. The results of these extended analyses demonstrated positive associations with respiratory disease and COPD mortality, which had not been previously evaluated among the ACS cohort. Similarly, Lepeule et al. (2012) reported the results of an extended analysis of the Harvard Six Cities cohort, extending the follow-up period to include deaths between 1974 and 2009. This was the first time that COPD mortality was evaluated among the Harvard Six Cities cohort; the relative risk was positive, but imprecise due to the smaller number of COPD deaths compared to deaths from other causes.

Several additional U.S. cohort studies evaluated the association between long-term $PM_{2.5}$ exposure and respiratory mortality. In a nationwide cohort of older Americans, Thurston et al. (2015) used monthly estimates of $PM_{2.5}$ concentration to assign annual mean concentrations to participants in the NIH-AARP cohort study and observed a positive association with respiratory mortality. The California Teachers Study (Lipsett et al., 2011; Ostro et al., 2010) examined the association between $PM_{2.5}$ and mortality among female public-school teachers and observed positive associations between long-term $PM_{2.5}$ exposure and respiratory mortality. In a reanalysis of the cohort with refined exposure assessment, Ostro et al. (2015) used a chemical transport model (CTM) to predict $PM_{2.5}$ concentrations with a 4-km spatial resolution, observing a null association between $PM_{2.5}$ exposure and respiratory mortality. Hart et al. (2011) examined the association between residential exposure to $PM_{2.5}$ estimated from a single year of monitoring data (2000) and mortality among men in the U.S. trucking industry in the Trucking Industry Particle Study (TrIPS). The results for respiratory mortality were similar to those reported by Lipsett et al. (2011) for respiratory mortality. The results for COPD mortality were null for the cohort and positive, though imprecise for a sensitivity analyses excluding long-haul drivers.



CanCHEC = Canadian Census Health and Environment Cohort; IQR = interquartile range; TrIPS = Trucking Industry Particle Study; NIH-AARP = National Institutes of Health American Association of Retired Persons Diet and Health Cohort; ACS = American Cancer Society Cohort; CCHS = Canadian Community Health Survey; LUR-BME = land use regression-Bayesian maximum entropy exposure model.

Note: †Studies published since the 2009 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Study results from Lepeule et al. (2012) are representative of results from the Harvard Six Cities Cohort; Study results from Turner et al. (2016) are representative of the results from the American Cancer Society Cohort.

Figure 5-34 Associations between long-term exposure to $PM_{2.5}$ and respiratory mortality in recent North American cohorts.

In an extended reanalysis of the Canadian CanCHEC cohort Crouse et al. (2015) observed associations for respiratory and COPD mortality that were just below the null value. The general pattern and magnitude of these associations were generally unchanged in cumulative risk models that include O_3 and/or NO_2. Pinault et al. (2016) linked a subset of participants from the CanCHEC cohort to the Canadian Community Health Survey and observed positive associations with respiratory mortality. Pinault et al. (2016) was able to make use of the individual-level covariate data on age, sex, smoking, alcohol consumption, obesity, and fruit/vegetable consumption that was not available in the larger

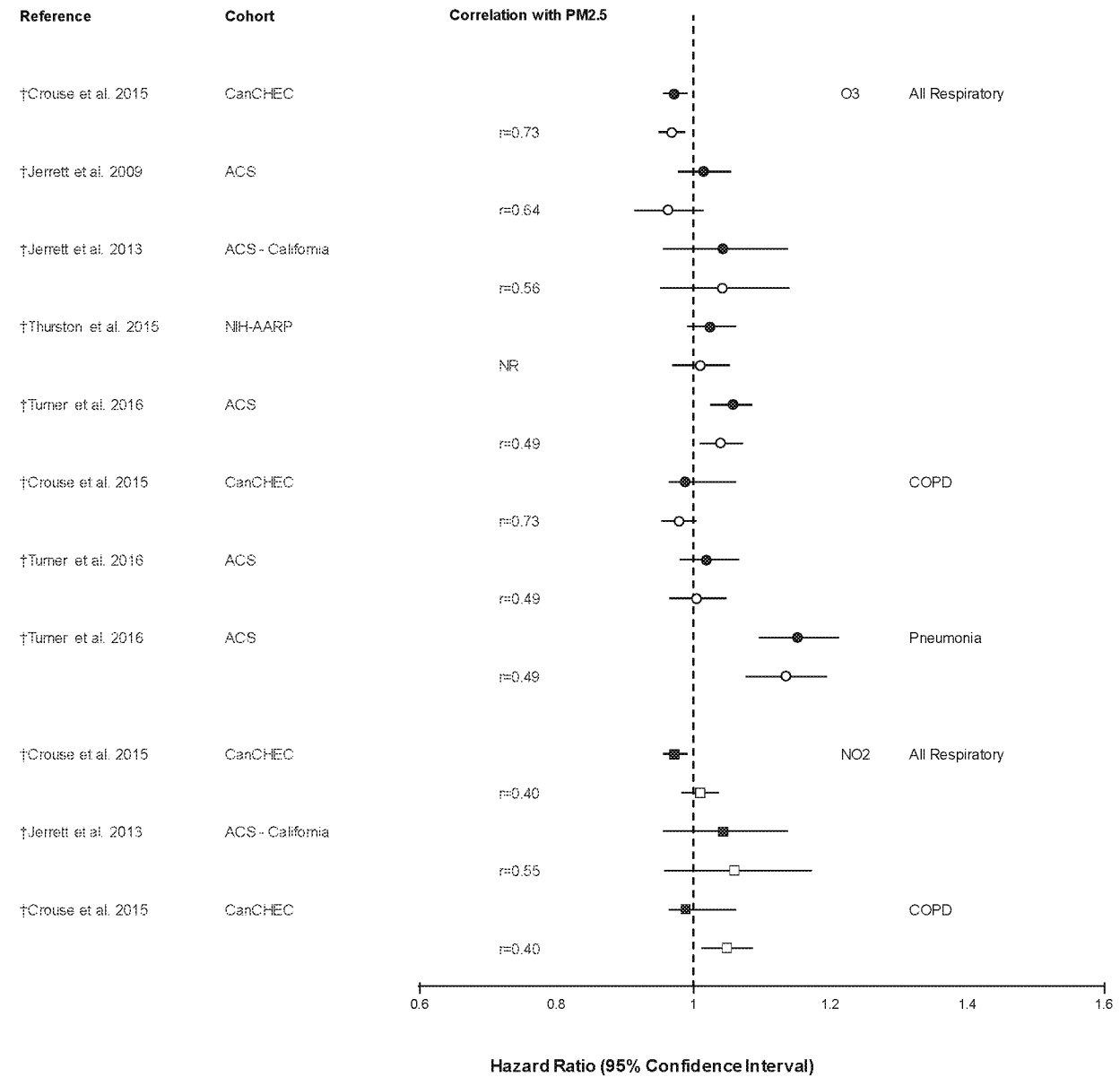
CanCHEC cohort. The inclusion of these individual-level data may help to explain the inconsistent results observed by Crouse et al. (2015) and Pinault et al. (2016).

Overall, the results of these recent U.S. cohort studies demonstrate a generally consistent, positive association between long-term $PM_{2.5}$ exposure and respiratory mortality, though the results from the two Canadian studies are inconsistent. In addition, a study conducted in Europe that pooled data from 22 existing cohort studies and evaluated the association between long-term $PM_{2.5}$ exposure and respiratory mortality observed an association for respiratory mortality near the null value (Dimakopoulou et al., 2014). The associations for respiratory mortality in analysis of pooled data were generally positive, though some inconsistencies among the results from different analyses of the same cohort provide some uncertainty in the stability of these results (Pinault et al., 2016; Crouse et al., 2015; Ostro et al., 2015; Ostro et al., 2010). Recent studies have evaluated the association between long-term $PM_{2.5}$ exposure and COPD mortality, a cause of death for which there has previously been little examination. These studies report modest positive associations with COPD mortality and the hazard ratios are generally less precise than those for respiratory mortality. A single study (Turner et al., 2016) examined deaths due to respiratory infection and long-term $PM_{2.5}$ exposure and observed a positive association.

5.2.10.1 Potential Copollutant Confounding of the $PM_{2.5}$-Mortality Relationship

In the examination of potential confounding effects of copollutants on the relationship between long-term $PM_{2.5}$ exposure and respiratory mortality, it is informative to evaluate whether $PM_{2.5}$ risk estimates are changed in copollutant models. Recent studies have examined the potential for copollutant confounding by evaluating copollutant models that include O_3 and NO_2 (Figure 5-35). These recent studies address a previously identified data gap by informing the extent to which effects associated with exposure to $PM_{2.5}$ are independent of coexposure to correlated copollutants in long-term analyses.

The results for associations between long-term $PM_{2.5}$ exposure and respiratory mortality in single pollutant models and copollutant models adjusted for O_3 and NO_2 are shown in Figure 5-35. The correlations between $PM_{2.5}$ and O_3 exposures in the studies that conducted copollutant analyses were generally positive and moderate to strong, ranging from $r = 0.49$ to 0.73. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for O_3. The associations persisted across different specific causes of respiratory mortality. The correlations between $PM_{2.5}$ and NO_2 exposures in studies that conducted copollutant analyses were positive and moderate ($r = 0.40$; $r = 0.55$). In one study (Jerrett et al., 2013), the $PM_{2.5}$ effect estimates remained relatively unchanged in a copollutant model adjusted for NO_2, while in another (Crouse et al., 2015), the $PM_{2.5}$ estimates increased and changed from negative to positive after adjusting for NO_2 for respiratory and COPD mortality.



ACS: American Cancer Society Cohort; CanCHEC = Canadian Census Health and Environment Cohort; AHSMOG = Adventist Health Air Pollution Study; COPD = chronic obstructive pulmonary disease; NR = not reported.

Note: †Studies published since the 2009 PM ISA. Circles and squares represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled symbols represent effect of $PM_{2.5}$ in single pollutant models, open circles represent effect of $PM_{2.5}$ adjusted for O_3; open squares represent effect of $PM_{2.5}$ adjusted for NO_2. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

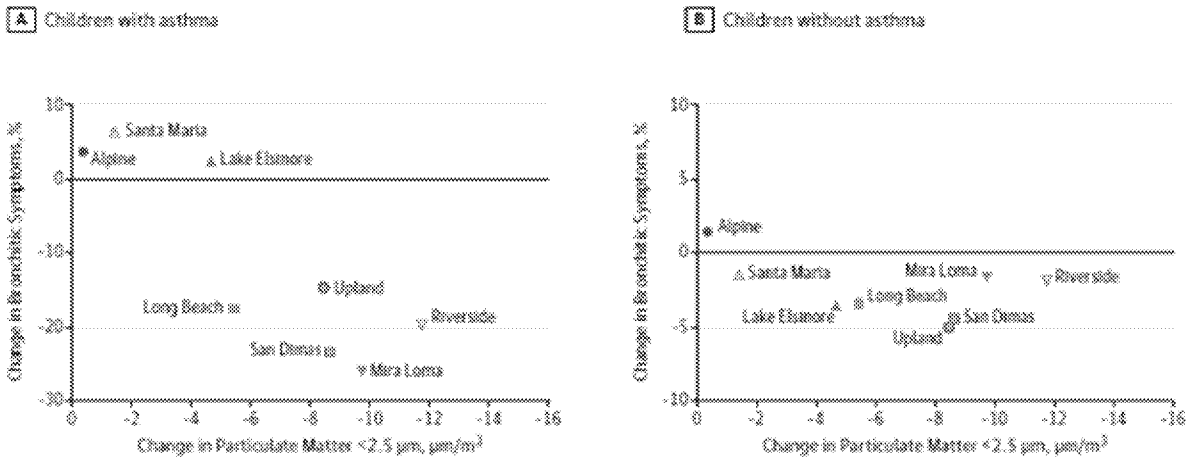
Figure 5-35 Long-term exposure to $PM_{2.5}$ and mortality in single pollutant models and models adjusted for ozone or nitrogen dioxide.

5.2.11 Respiratory Effects and Declining $PM_{2.5}$ Concentrations

In the 2009 PM ISA (U.S. EPA, 2009), none of the reviewed studies related declining concentrations of long-term $PM_{2.5}$ to respiratory health endpoints. A reduction in air pollution can restore "biological normality by removal of an abnormal exposure" (Rose, 1981). In populations, this has been shown to lead to a reduction of risk in a large number of people and result in a decline in cases of respiratory disease or improved lung function and development. Recent studies examine $PM_{2.5}$ decreases and improvements in respiratory health in children and adults. The majority of this recent evidence comes from prospective cohort studies of decreased $PM_{2.5}$ concentrations in CHS communities that observed improved respiratory health in children (Berhane et al., 2016; Gauderman et al., 2015).

5.2.11.1 Bronchitis

Since the beginning of the CHS studies, pollutant levels have been declining in the CHS southern California communities. Recently, Berhane et al. (2016) prospectively examined the relationship between declining pollutant levels and self-reported chronic bronchitis symptoms in three cohorts of children (n = 4,602) in eight communities. From 1992 to 2012, mean $PM_{2.5}$ concentrations declined across all communities from 20.5 to 14.4 $\mu g/m^3$. Due to significant differences in chronic bronchitis prevalence by asthma status, the authors presented separate results for children without asthma and children with asthma. As depicted in Figure 5-36, communities with greater reductions of $PM_{2.5}$ had larger unadjusted reductions of bronchitis symptoms. The relationship was noticeably stronger in children with asthma. In adjusted models, a 5 $\mu g/m^3$ decrease in $PM_{2.5}$ was associated with a 25% (95% CI: 11, 37%) decrease in odds of bronchitic symptoms in 10-year old children with asthma. Berhane et al. (2016) also observed decreases in bronchitic symptoms in 10-year olds without asthma (OR = 0.84 [95% CI: 0.76, 0.93] per 5 $\mu g/m^3$ decrease in $PM_{2.5}$). The observed associations were relatively unchanged in copollutant models controlling for O_3 ($r = 0.54$). Copollutant models with other pollutants were not examined due to high correlations (NO_2: $r = 84$; PM_{10}: $r = 0.88$). Meanwhile, observed decrements in bronchitic symptoms in 15-year olds were similar, but slightly stronger than those seen in 10-year-olds.

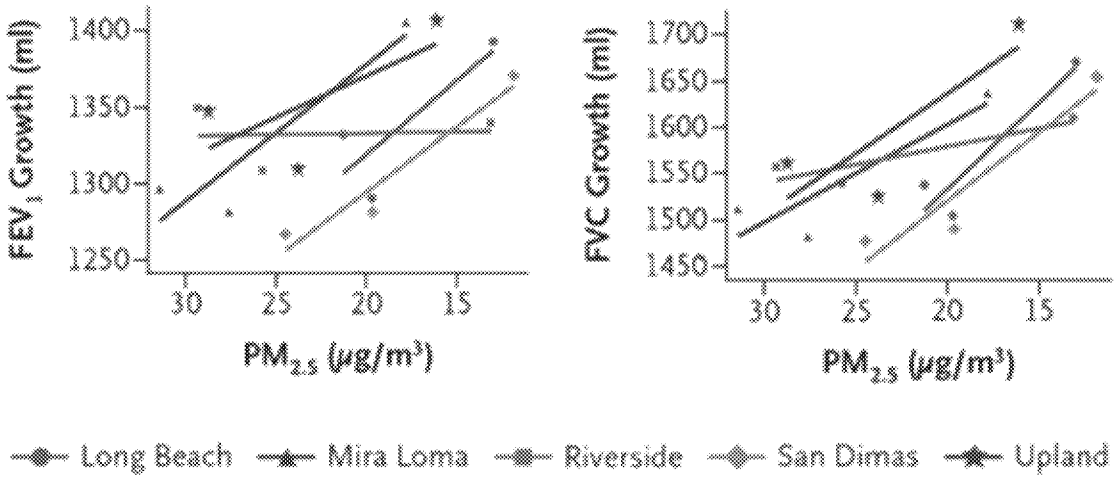


Source: Permission pending, Berhane et al. (2016).

Figure 5-36 Estimated bronchitic symptom prevalence at age 10 versus mean air pollutant concentrations among Children's Health Study (CHS) participants by asthma status.

5.2.11.2 Pulmonary Function

A recent study combined data obtained from three separate CHS cohorts to examine the association between long term reductions in air pollution and lung development in children between the ages of 11 and 15 (Gilliland et al., 2017; Gauderman et al., 2015). Study specific details, including results, are presented in Table 5-19 (Section 5.2.2.1). Briefly, the study sample included children recruited from three separate CHS cohorts spread out over a 20-year period. The analysis was restricted to the five study communities (Long Beach, Mira Loma, Riverside, San Dimas, and Upland) in which pulmonary function testing was performed in all three cohorts (n = 2,120). Significant improvements in lung-function growth were observed within and across communities as air quality improved over the study period (see Figure 5-37 for unadjusted relationship and Table 5-19 for fully-adjusted model results).



Note: The 4-year mean growth in forced expiratory volume in 1 second (FEV_1) and the mean growth in forced vital capacity (FVC) from 11 to 15 years of age are plotted against the corresponding levels of $PM_{2.5}$ for each community and cohort.
Source: Permission pending, Gauderman et al. (2015).

Figure 5-37 Mean 4-year lung-function growth versus the mean levels of $PM_{2.5}$.

A similar study examined the impact of improved air quality on lung function in adults (Boogaard et al., 2013). Boogaard et al. (2013) conducted a small population-based study in the Netherlands, aiming to describe the effect of traffic policy-related reductions in air pollution in 12 locations in the Netherlands (8 urban, 4 suburban). Study details and results are presented in Table 5-20 (Section 5.2.2.2). In summary, baseline lung function was measured in 746 participants prior to implementation of a low emission zone traffic policy. Lung function was measured again at follow-up, 2 years after policy implementation (87% follow-up). In adjusted analyses, 2-year declines in $PM_{2.5}$ were associated with increases in FVC and decreases in airway resistance, indicating improvements in lung function associated with reductions in $PM_{2.5}$.

5.2.11.3 Summary

Initial studies examining the relationship between improvements in air quality and whether this resulted in beneficial changes in respiratory effects observed a consistent relationship between decreasing $PM_{2.5}$ concentrations and improved respiratory health. These results provide corroborating evidence of an association between $PM_{2.5}$ and lung development (Section 5.2.2) and bronchitis (Section 5.2.5). Examination of potential copollutant confounding was limited, but there was evidence that the $PM_{2.5}$ effect was robust in models including O_3 (Berhane et al., 2016).

5.2.12 Associations Between $PM_{2.5}$ Components and Sources and Respiratory Effects

The 2009 PM ISA (U.S. EPA, 2009) did not include an organized discussion of the potential relationship between long-term exposure to $PM_{2.5}$ components and respiratory effects. The limited number of available studies found some evidence of an association between respiratory health and exposure to elemental and organic carbon (EC and OC), but no studies examining metals were available. In addition to constituting a small body of evidence, the EC and OC results did not adjust for $PM_{2.5}$ mass, which raises additional uncertainties considering that EC and OC are components within the complex mixture that is $PM_{2.5}$, and the generally high correlations ($r > 0.7$) between EC, OC, and $PM_{2.5}$. Since the completion of the 2009 PM ISA, a number of recent studies have further examined $PM_{2.5}$ components, including metals, and a limited number of these studies have attempted to control for potential confounding by $PM_{2.5}$ mass. In addition to studies of carbon fractions and metals, a recent study also examined respiratory health effects related to the oxidative potential (OP) of $PM_{2.5}$. Due to a limited number of studies for most individual components, and even fewer studies for any given endpoint, no single component is identified as having a stronger relationship with respiratory effects or one that clearly differs from that of $PM_{2.5}$ total mass. All of the studies presented in Table 5-27 are discussed in greater detail throughout this chapter, such that the discussion in this section will not focus on specific study details unless they are specifically relevant to interpretation of $PM_{2.5}$ component results.

Figure 5-38 charts the trend of results for $PM_{2.5}$ mass and individual $PM_{2.5}$ components studies detailed in Table 5-27. The focus of the figure and the ensuing discussion is on studies of lung function and asthma, for which there is evidence of an association with long-term exposure to $PM_{2.5}$. Where available, the chart reflects $PM_{2.5}$ mass-adjusted component results.

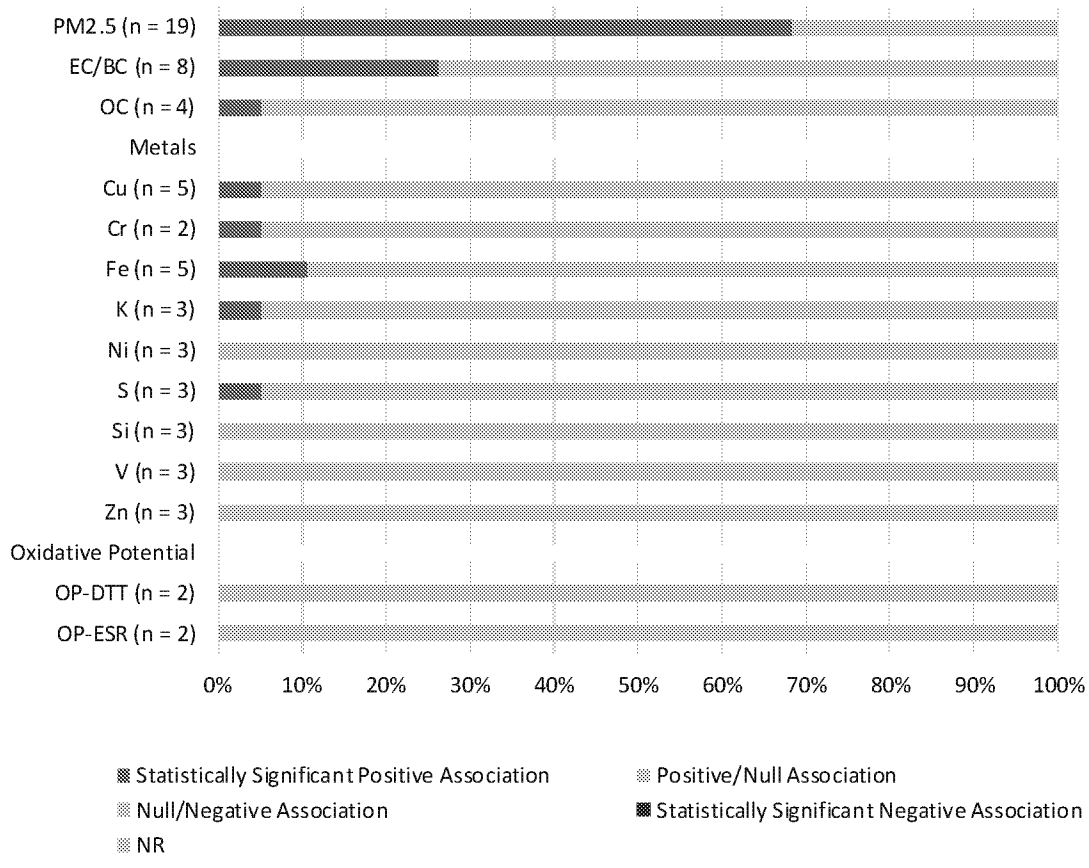
Table 5-27 Heat map of associations observed between long-term exposure $PM_{2.5}$ and $PM_{2.5}$ components and respiratory health.

Study	Endpoint	$PM_{2.5}$	EC/BC	OC	Cu	Cr	Fe	K	Ni	S	Si	V	Zn	OP^{DTT}	OP^{ESR}
Lung Function and Development															
Gauderman et al. (2004)	FEV_1 Growth														
†Breton et al. (2011)	FEV_1														
†Gehring et al. (2015a)	FEV_1														
†Eeftens et al. (2014)	FEV_1														
†Eeftens et al. (2014)‡	FEV_1														
†Yang et al. (2016)	FEV_1														
†Yang et al. (2016)‡	FEV_1														
†Boogaard et al. (2014)	FVC														
†Boogaard et al. (2014)	Airway Resistance														
Asthma															
Islam et al. (2007)	Asthma Incidence														
†Gehring et al. (2015a)	Asthma Incidence														
†Clark et al. (2013)	Asthma Incidence														
†Carlsten et al. (2011)	Asthma Incidence														
†Yang et al. (2016)	Asthma Incidence														
†Yang et al. (2016)‡	Asthma Incidence														
†Chiu et al. (2014)	Wheeze														
Other															
Kim et al. (2004)	Bronchitis														
McConnell et al. (2003)	Bronchitic Symptoms														
McConnell et al. (2003)‡	Bronchitic Symptoms														
†Fuertes et al. (2014)[a]	Pneumonia														
†Fuertes et al. (2014)[a]‡	Pneumonia														
†Karr et al. (2009)	Infant bronchiolitis														
†Gan et al. (2013)	COPD														

[a]$PM_{2.5}$ estimate came from a different study of the same cohort (Eeftens et al., 2014).

‡Associations adjusted for $PM_{2.5}$ mass.

Note: † $PM_{2.5}$ component studies published since the 2009 PM ISA. Dark blue = study reported statistically significant association between $PM_{2.5}$/component and impaired respiratory health outcome; light blue = study reported association between $PM_{2.5}$/component and impaired respiratory health outcome regardless of width of confidence intervals; light orange = study reported null or inverse association; red = study reported statistically significant association between $PM_{2.5}$/component and improved respiratory health outcome; gray = study did not examine individual component. Studies sorted by outcome.



Note: Bars represent the percentage of results for $PM_{2.5}$ mass or $PM_{2.5}$ components from lung function and asthma studies detailed in Table 5-27 that show statistically significant impaired respiratory health (dark blue), impaired respiratory health (light blue), null/improved respiratory health (light orange), or statistically significant improved respiratory health (red). n = number of estimates across the studies detailed in Table 5-27 for $PM_{2.5}$ mass or the individual $PM_{2.5}$ components. When available, this figure uses $PM_{2.5}$ mass-adjusted component associations. See Table 5-27 for more details.

Figure 5-38 Distribution of associations for $PM_{2.5}$ and $PM_{2.5}$ components examined in studies detailed in Table 5-27.

5.2.12.1 Elemental Carbon, Black Carbon, and Organic Carbon

As discussed in the 2009 PM ISA (U.S. EPA, 2009), Gauderman et al. (2004) examined the relationship between lung function growth and long-term exposure to EC and OC. The authors observed evidence of an association between EC and OC exposure and lung development in children, as measured by 8-year growth in FEV_1, FVC, and MMEF. In a recent, expanded CHS analysis examining an additional cohort, Breton et al. (2011) observed similar results to Gauderman et al. (2004). However, $PM_{2.5}$ effects were noted in both studies, and EC and OC were highly correlated with $PM_{2.5}$ ($r = 0.91$ for both components), adding uncertainty to the independent effect of either component. Results from a limited number of recent studies also suggest a potential link between EC and asthma incidence in children. However, the results are not as consistent as those for $PM_{2.5}$.

5.2.12.2 Metals

Elemental fractions of $PM_{2.5}$ were examined as predictors of lung function in two European cohort studies (Gehring et al., 2015a; Eeftens et al., 2014). In an ESCAPE project analysis of 6- to 8-year-old children in five European birth cohorts, Eeftens et al. (2014) reported small reductions in FEV_1, between 0.5 and 1.5%, associated with IQR increases in Cu, Fe, Ni, S, and V. However, after adjustment for $PM_{2.5}$ mass, all negative associations were null except for Fe and S. Similar single-pollutant results were noted in 8- to 12-year-old children in the PIAMA cohort (Gehring et al., 2015a), which was also included in the ESCAPE analysis. The authors did not report $PM_{2.5}$-mass adjusted results. Gehring et al. (2015a) also reported associations between all of the examined metals and asthma incidence (Cu, Fe, K, Ni, S, Si, V, and Zn).

As discussed previously for EC and OC, moderate to high correlations with $PM_{2.5}$, as well as negated effects in models adjusting for $PM_{2.5}$, indicate uncertainty about the independence of the observed associations between elemental fractions of $PM_{2.5}$ and respiratory health. Additionally, the ESCAPE cohorts, including PIAMA, implemented LUR models to estimate exposure to $PM_{2.5}$ components. The models predicted concentration variance with varying degrees of accuracy (R^2 = 0.53−0.79), potentially introducing more exposure measurement error for some components compared to others (de Hoogh et al., 2013). Overall, explained variance was generally higher for $PM_{2.5}$ mass compared to components, indicating greater confidence in the $PM_{2.5}$ concentrations as compared to components.

5.2.12.3 Oxidative Potential

Information from recent studies on the oxidative potential (OP) of $PM_{2.5}$ (i.e., the inherent capacity of PM to generate reactive oxygen species) is presented in a study of the PIAMA cohort in the Netherlands (Yang et al., 2016). The authors propose a link between oxidative potential of $PM_{2.5}$, $PM_{2.5}$ exposure, oxidative stress and inflammation, and respiratory health effects. Yang et al. (2016) reported associations with asthma incidence and lung function decrements (FEV_1 and FVC). Results were dependent on the methods used to quantify OP, with health effects observed with OP measured using the dithiothreitol assay, but null effects for OP measured using spin resonance assay. Results also differed by exposure period, with stronger associations generally observed between the aforementioned respiratory health effects and OP estimated (by LUR) for the concurrent period, compared to OP estimated at participants' birth address. Asthma and lung function associations with OP persisted with adjustment in two-pollutant models for $PM_{2.5}$, NO_2, and a number of $PM_{2.5}$ metals.

5.2.12.4 Summary

Overall, recent studies add evidence for respiratory effects related to long-term $PM_{2.5}$ component exposures. However, evidence remains limited for any component being more strongly associated with a specific respiratory effect compared to $PM_{2.5}$ mass. Additionally, due to generally high component correlations with $PM_{2.5}$ mass, it is uncertain whether the exposure estimates adequately represent exposure to the components rather than a marker for $PM_{2.5}$, which is more strongly associated with respiratory health effects across a large number of studies.

5.2.13 Summary and Causality Determination

The 2009 PM ISA (U.S. EPA, 2009) evaluated long-term $PM_{2.5}$ exposure and respiratory effects and concluded that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and respiratory effects (U.S. EPA, 2009).[58] This conclusion was based mainly on epidemiologic evidence demonstrating associations between long-term $PM_{2.5}$ exposure and changes in lung function or lung function growth rate in children. Correlations of $PM_{2.5}$ concentrations with concentrations of other air pollutants, and a limited number of studies that examined potential copollutant confounding, made the interpretation of epidemiologic results more challenging. However, the consistency of findings across different locations supported an independent effect of $PM_{2.5}$. Biological plausibility was provided by a single animal toxicological study involving pre- and -post-natal exposure to $PM_{2.5}$ CAPs which found impaired lung development. Recent studies enhance the evidence base. The evidence for the relationship between long-term exposure to $PM_{2.5}$ and respiratory effects is summarized in Table 5-28, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

[58] As detailed in the Preface , risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations unless otherwise noted.

Table 5-28 Summary of evidence for a likely to be causal relationship between long-term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Lung function and development			
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Studies provide evidence of decrements in lung function growth and for decrements in attained lung function in children in multiple cohorts.	Children: Gauderman et al. (2015); Gehring et al. (2015a); Gauderman et al. (2004)	Children: CHS community mean concentration range: 6–28 µg/m^3 PIAMA Cohort: 16.4 µg/m^3
	Associations are also observed for $PM_{2.5}$-related acceleration of lung function decline in adults.	Adults: Rice et al. (2015a) Adam et al. (2015) Section 5.2.2	Adults: Framingham: 10.8 µg/m^3 ESCAPE Range: 9.5–17.8 µg/m^3
	Supporting evidence is provided by improvements in lung function growth associated with declining $PM_{2.5}$ concentrations.	Gauderman et al. (2015) Boogaard et al. (2013) Section 5.2.11	
Limited evaluation of confounding by copollutants	Potential copollutant confounding for lung function growth is examined in a limited number of studies, with some evidence that associations remain robust in models with gaseous pollutants. However, there is uncertainty regarding studies in Asia due to high annual $PM_{2.5}$ concentrations.	Hwang et al. (2015) Gehring et al. (2013) Wang et al. (2015b)	
Limited evidence from toxicological studies at relevant concentrations	Pre- and post-natal exposure to ambient levels of urban particles impaired mouse lung development.	Mauad et al. (2008)	17 µg/m^3
Biological plausibility	Evidence from an animal toxicological study provides biological plausibility for epidemiologic findings for lung function growth.	Section 5.2.1	

Table 5-28 (Continued): Summary of evidence for a likely to be causal relationship between long term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Development of asthma			
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Longitudinal studies provide evidence of associations with asthma incidence in children.	Carlsten et al. (2011) Tétreault et al. (2016a) Gehring et al. (2015b) Section 5.2.3.1	5.2–16.5 $\mu g/m^3$
	Supporting evidence is provided by studies of asthma prevalence in children and by studies of childhood wheeze.	Chiu et al. (2014) Section 5.2.3.1	11.2 $\mu g/m^3$
Limited evaluation of confounding by copollutants	Potential copollutant confounding for asthma incidence in children is examined in a single study, with limited evidence that associations remain robust in models with NO_2.	MacIntyre et al. (2014a)	
Coherence in epidemiologic studies across the continuum of effects	Supporting evidence provided by associations with eNO, a marker of pulmonary inflammation.	Dales et al. (2008) Berhane et al. (2014)	
Limited evidence from toxicological studies at relevant concentrations	Results show the development of an allergic Th2 phenotype, increased bronchial obstruction, and collagen deposition in the lungs of DEP-exposed mice.	Kim et al. (2016a)	100 $\mu g/m^3$
Biological plausibility	Evidence from an animal toxicological study provides biological plausibility for epidemiologic findings for the development of asthma.	Section 5.2.3.3	
Respiratory effects in healthy populations			
Strong evidence from toxicological studies at relevant concentrations	Results show oxidative stress, inflammation, and morphologic changes in both the upper (nasal) and lower airways. Upregulation of the RAS was also found. Other results relevant to the development of asthma, allergic disease, and COPD and to impaired lung development are mentioned above.	Section 5.2.8	61–200 $\mu g/m^3$

Table 5-28 (Continued): Summary of evidence for a likely to be causal relationship between long term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Respiratory mortality			
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Cohort studies show associations for respiratory mortality and cause-specific respiratory mortality, including COPD and infection.	Thurston et al. (2015) Lipsett et al. (2011) Ostro et al. (2010) Hart et al. (2011) Pinault et al. (2016) Crouse et al. (2015) Turner et al. (2016) Pope et al. (2014) Lepeule et al. (2012)	10.2–13.6 μg/m^3 15.6 μg/m^3 17.0 μg/m^3 14.1 μg/m^3 6.3 μg/m^3 8.9 μg/m^3 12.6 μg/m^3 12.6μg/m^3 11.4–23.6 μg/m^3
Uncertainty regarding confounding by copollutants and exposure measurement error	Potential copollutant confounding is examined in a few studies with some evidence that associations remained robust in models with gaseous pollutants. Exposure measurement error is less likely for long-term $PM_{2.5}$ compared with shorter averaging times and other size fractions.	Section 5.2.10	
Some coherence with underlying causes of mortality	COPD evidence provides coherence with respiratory mortality.	Section 5.2.6	
Other respiratory endpoints			
Limited epidemiologic evidence from studies of allergic disease, severity of respiratory disease, and COPD development	Generally consistent evidence of an association for allergic sensitization. However, consistent associations with specific allergens have not emerged.	Gruzieva et al. (2014) Gehring et al. (2010) Weir et al. (2013) Section 5.2.4	12.7–16.9 μg/m^3
	Limited evidence of increased bronchitic symptoms and increased hospitalizations in children with asthma.	McConnell et al. (2003) Tétreault et al. (2016b) Section 5.2.7	9.9–13.8 μg/m^3
	Cohort studies provide some evidence of associations with COPD development.	Atkinson et al. (2015) Gan et al. (2013) To et al. (2015) Section 5.2.5	4.1–12.5 μg/m^3

Table 5-28 (Continued): Summary of evidence for a likely to be causal relationship between long term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Coherence of related effects across disciplines	Evidence from an animal toxicological study provides coherence with epidemiologic findings for the development of an allergic phenotype.	Kim et al. (2016a)	100 μg/m^3
	Exposure to DEP did not worsen the asthma phenotype.	Farraj et al. (2010)	2,000 μg/m^3
Other uncertainties	Studies of COPD development and severity of respiratory disease may not account for the potential effect of short-term exposures leading to these acute events.	Section 5.2.5 Section 5.2.7	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

Multiple cohort studies measuring lung function development over time continue to support the relationship between long-term $PM_{2.5}$ exposure and decrements in lung function growth, providing evidence for a robust and consistent association across study locations, exposure assessment methods, and time periods (Section 5.2.2). The relationship between $PM_{2.5}$ and lung function development is further supported by a recent study that related declining $PM_{2.5}$ concentrations to improvements in pulmonary function growth. Epidemiologic studies also examined asthma development in children (Section 5.2.3). A few recent prospective cohort studies in children found generally positive associations, but several are imprecise (i.e., reporting wide confidence intervals). Supporting evidence is provided by studies of asthma prevalence in children, by studies of childhood wheeze, and by studies of eNO, a marker of pulmonary inflammation. A recent animal toxicological study showing the development of an allergic phenotype and an increase in a marker of airway responsiveness provides biological plausibility for allergic asthma. One epidemiologic study reports a copollutant model with NO_2, in which the $PM_{2.5}$ effect persisted. Other epidemiologic studies focusing on lung function in adults and report a $PM_{2.5}$-related acceleration of lung function decline in adults, while improvement was observed with declining $PM_{2.5}$ concentrations (Section 5.2.11). Declining $PM_{2.5}$ concentrations are also associated with an improvement in chronic bronchitis symptoms in children in a recent longitudinal study, strengthening evidence reported in the 2009 PM ISA for a relationship between increased chronic bronchitic symptoms and long-term $PM_{2.5}$ exposure (Section 5.2.11).

A common uncertainty across the epidemiologic studies is the lack of examination of copollutants to assess the potential for confounding. While there is some evidence that associations remain robust in models with gaseous pollutants, a number of studies examining copollutant confounding are conducted in Asia, and thus have limited generalizability due to high annual pollutant concentrations. Exposure measurement error is less likely for long-term $PM_{2.5}$ compared with shorter averaging times and other size fractions (Section 3.4.5). Animal toxicological studies continue to provide evidence that long-term exposure to $PM_{2.5}$ results in a variety of respiratory effects. Recent studies show pulmonary oxidative stress, inflammation, and morphologic changes in the upper (nasal) and lower airways. Other results show changes consistent with the development of allergy and asthma and impaired lung development, which are mentioned above. **Overall, the collective evidence is sufficient to conclude that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and respiratory effects.**

5.3 Short-Term $PM_{10-2.5}$ Exposure and Respiratory Effects

The 2009 PM ISA (U.S. EPA, 2009) concluded that the relationship between short-term exposure to $PM_{10-2.5}$ and respiratory effects is "suggestive of a causal relationship" (U.S. EPA, 2009), based on a limited number of epidemiologic studies supporting associations with some respiratory effects and a limited number of experimental studies that provide biological plausibility.[59] Epidemiologic findings were consistent for hospital admissions and ED visits for respiratory infection and respiratory-related diseases, but not for COPD. Evidence that short-term $PM_{10-2.5}$ exposure exacerbates asthma was inconsistent in epidemiologic studies. In addition, these studies were characterized by overall uncertainty in the exposure assignment approach. Limited information was available regarding potential copollutant confounding across the array of respiratory effects examined. Controlled human exposure studies of short-term $PM_{10-2.5}$ exposure found no lung function decrements and inconsistent evidence for pulmonary inflammation in healthy individuals or human subjects with asthma. Animal toxicological studies were limited to those using noninhalation (e.g., intra-tracheal instillation) routes of $PM_{10-2.5}$ exposure.

Recent epidemiologic findings more consistently link $PM_{10-2.5}$ to asthma exacerbation, and a recent controlled human exposure study in individuals with asthma found pulmonary inflammation and other alterations of the immune system following short-term exposure to $PM_{10-2.5}$ CAPs (Section 5.3.2). Recent animal toxicological studies use noninhalation routes of $PM_{10-2.5}$ exposure and demonstrate enhanced allergic responses in models of allergic airway disease, which share phenotypic features with asthma in humans. Recent epidemiologic findings are more consistent than previous findings for COPD exacerbation (Section 5.3.3), consistent with previous findings for respiratory-related diseases (Section 5.3.5), and somewhat inconsistent with previous findings for respiratory infection (Section 5.3.4). Respiratory effects related to short-term $PM_{10-2.5}$ exposure in healthy people remain

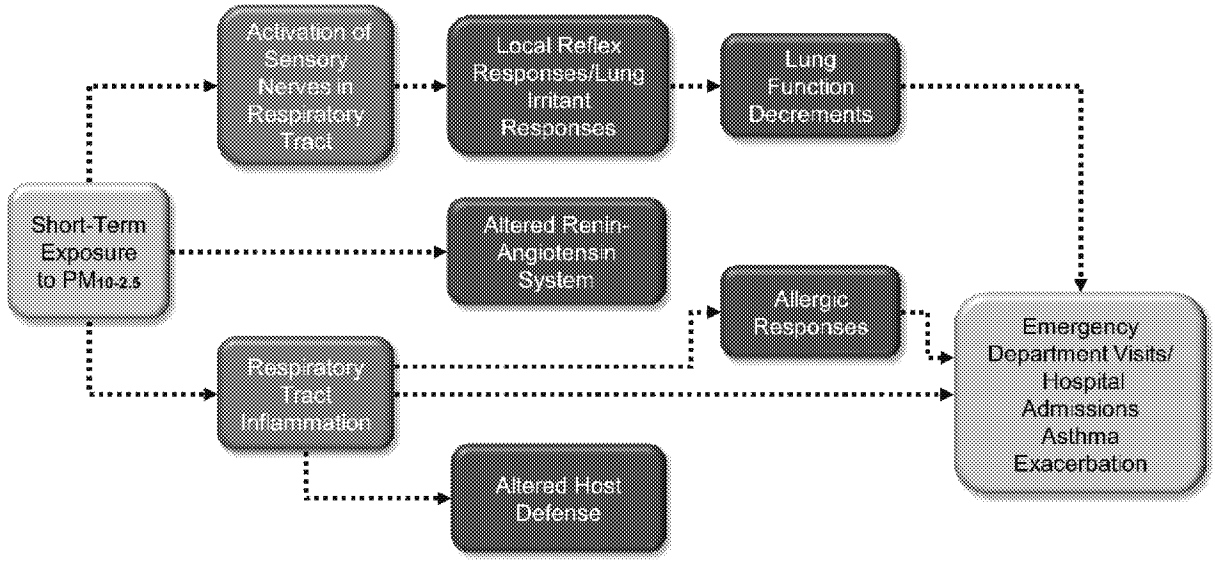
[59] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{10-2.5}$ concentrations unless otherwise noted.

uncertain (Section 5.3.6). Evidence from recent epidemiologic studies is inconsistent. A controlled human exposure study found no evidence for changes in lung function. In contrast, a few recent studies involving short-term inhalation exposure of rodents showed decreased lung function and increased pulmonary inflammation.

Previous epidemiologic studies using a single dichotomous $PM_{10-2.5}$ monitor or averaging across monitors to obtain an estimate for $PM_{10-2.5}$ concentration likely have more uncertainty in the exposure surrogate compared with $PM_{2.5}$, given spatiotemporal variability in ambient $PM_{10-2.5}$ concentrations (Section 3.3.1.1 and Section 3.4.2.2). Uncertainties were compounded for previous epidemiologic studies that estimate $PM_{10-2.5}$ concentration as the difference between PM_{10} concentration and $PM_{2.5}$ concentration from monitors that were not collocated. For asthma exacerbation, recent epidemiologic studies have improved exposure assessment with $PM_{10-2.5}$ measurements in subjects' microenvironments using personal samplers. However, across respiratory outcome groups, uncertainties remain regarding copollutant confounding.

5.3.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory health effects resulting from short-term exposure to $PM_{10-2.5}$. Figure 5-39 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" short-term exposure to $PM_{10-2.5}$ may lead to respiratory health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.3.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-39 Potential biological pathways for respiratory effects following short-term $PM_{10-2.5}$ exposure.

Once $PM_{10-2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). Insoluble and soluble components of $PM_{10-2.5}$ may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential." Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.

Evidence that short-term exposure to $PM_{10-2.5}$ may affect the respiratory tract generally informs two proposed pathways (Figure 5-39). The first pathway begins with injury, inflammation, and oxidative stress responses, which are difficult to disentangle. Inflammation generally occurs as a consequence of injury and oxidative stress, but it may also lead to further oxidative stress and injury due to secondary production of ROS by inflammatory cells. The second pathway begins with the activation of sensory

nerves in the respiratory tract that can trigger local reflex responses and transmit signals to regions of the central nervous system that regulate autonomic outflow.

Injury, Inflammation and Oxidative Stress

Experimental evidence that short-term exposure to $PM_{10-2.5}$ may affect the respiratory tract by inflammation-mediated pathways is provided by a limited number of inhalation studies. In healthy human subjects, some studies involving short-term exposure to $PM_{10-2.5}$ CAPs found inflammatory responses (Graff et al., 2009; Alexis et al., 2006), while others did not (Behbod et al., 2013; Jr et al., 2004). In human subjects with asthma, Alexis et al. (2014) found increased neutrophils in the BW, increased cytokines in BALF and BW, decreased expression of markers of innate immune and antigen presentation cell surface receptors, and increased expression of inflammatory cell surface receptors and the low-affinity IgE receptor. These changes indicate that alterations in innate host defense and allergic responses may occur. However, no increased markers of airway inflammation or changes in lung function were found by Jr et al. (2004) in humans with asthma. Variability in results of studies that involved short-term exposure to $PM_{10-2.5}$ CAPs may reflect differences in concentration and sources of $PM_{10-2.5}$ present in the airshed. Some epidemiologic studies linked short-term exposure to $PM_{10-2.5}$ to eNO, a marker of airway inflammation, in healthy individuals (Matt et al., 2016; Kubesch et al., 2015) and in children with asthma (Sarnat et al., 2012). Inflammatory and allergic responses in the context of asthma provide plausibility for epidemiologic findings of hospital admissions and ED visits for asthma (Section 5.3.2.1).

Two recent inhalation studies in rodents demonstrated inflammatory responses (Aztatzi-Aguilar et al., 2015; Amatullah et al., 2012). Increases in BALF total cells and macrophages and increased tissue IL-6 levels were observed following short-term exposure to $PM_{10-2.5}$ CAPs. Since rodents are obligatory nasal breathers (as opposed to humans who are oro-nasal breathers), deposition of inhaled $PM_{10-2.5}$ is expected to primarily occur in the extrathoracic airways (i.e., the nose) of rodents and to result in a much smaller fraction deposited in the lower respiratory tract compared with humans. Supportive evidence for respiratory tract effects is provided by animal toxicological studies involving noninhalation routes of exposure (i.e., oropharyngeal aspiration, intra-nasal instillation, subcutaneous injection). Pulmonary injury, oxidative stress, inflammation, and morphological changes were observed in healthy animals and in an animal model of cardiovascular disease (Section 5.3.6.3). In models of allergic airway disease, exposure to $PM_{10-2.5}$ by noninhalation routes enhanced allergic responses (Kurai et al., 2016; McGee et al., 2015; Kurai et al., 2014; He et al., 2012). The enhancement of allergic responses may underly exacerbation of asthma resulting from short-term exposure to $PM_{10-2.5}$ (Section 5.3.2).

Activation of Sensory Nerves

One of the recent inhalation studies in rodents involving short-term $PM_{10-2.5}$ CAPs exposure demonstrated changes in lung function (Amatullah et al., 2012). Baseline total respiratory resistance and

the maximum response to methacholine were increased and quasi-static compliance was decreased. The rapid nature of the lung function responses, which indicate airway obstruction, seen in the study by Amatullah et al. (2012) (i.e., immediately following the 4-hour exposure) indicates that activation of sensory nerves in the respiratory tract, possibly in the nasal airways, and the triggering of local reflex responses may have contributed to the effects of $PM_{10-2.5}$. Activation of sensory nerves in the respiratory tract can also transmit signals to regions of the central nervous system that regulate autonomic outflow and influence all the internal organs, including the heart. No changes in heart rate or heart rate variability were observed, indicating that altered autonomic outflow to the heart did not occur. Findings of lung function changes in this experimental study provide plausibility for epidemiologic findings related to asthma exacerbation.

Aztatzi-Aguilar et al. (2015) also found changes in components of the RAS. The RAS and the sympathetic nervous system, which is one arm of the ANS, are known to interact in a positive feedback fashion (Section 8.1.2) with important ramifications in the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract in this study.

Summary

As described here, there are two proposed pathways by which short-term exposure to $PM_{10-2.5}$ may lead to respiratory health effects. One pathway involves respiratory tract inflammation and allergic responses, which are linked to asthma exacerbation. The second pathway involves the activation of sensory nerves in the respiratory tract leading to lung function decrements, which are also linked to asthma exacerbation. While experimental studies involving animals or human subjects contribute most of the evidence of upstream effects, epidemiologic studies found associations between short-term exposure to $PM_{10-2.5}$ and respiratory tract inflammation. Together, these proposed pathways provide biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.3.8).

5.3.2 Asthma Exacerbation

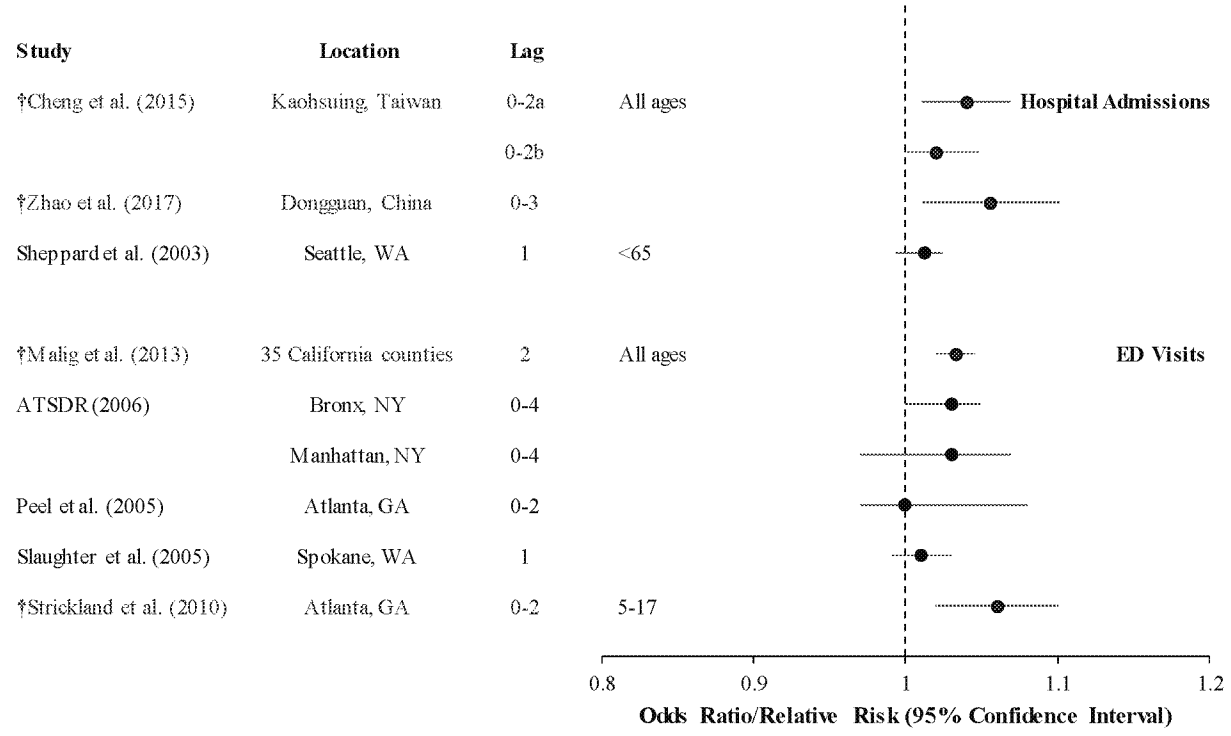
In the 2009 PM ISA (U.S. EPA, 2009), the evaluation of the relationship between short-term $PM_{10-2.5}$ exposure and asthma hospital admissions and ED visits was limited to single-city studies. These studies primarily focused on analyses of people of all ages, with a smaller number of studies examining associations in children and older adults. Across studies, there was inconsistent evidence of an association between short-term $PM_{10-2.5}$ exposure and asthma hospital admissions and between short-term $PM_{10-2.5}$ exposure and asthma ED visits, with some studies reporting evidence of a positive association while others did not. In addition, there was **limited epidemiologic evidence linking short-term $PM_{10-2.5}$ exposure and respiratory symptoms in children with asthma.** As detailed in Section 5.1.2, it is often

difficult to reliably diagnose asthma in children <5 years of age, potentially complicating the interpretation of results from studies that focus on $PM_{10-2.5}$ effects in children. **In the single controlled human exposure study which was evaluated, no evidence for decrements in pulmonary function or inflammation was found.**

5.3.2.1 Hospital Admissions and Emergency Department (ED) Visits

Recent epidemiologic studies continue to examine whether there is evidence of an association between short-term $PM_{10-2.5}$ exposure and asthma hospital admissions and ED visits, but the overall assessment remains limited to a small number of studies. Across studies, there is evidence of generally consistent, positive associations between $PM_{10-2.5}$ and asthma hospital admissions and between short-term $PM_{10-2.5}$ exposure and asthma ED visits (Figure 5-40). The results from asthma hospital admission and ED visit studies in children are supported by a study focusing on asthma physician visits in Atlanta, for the initial time period of the study, but this pattern of associations was not observed for the later time period at lag 3−5 days (Sinclair et al., 2010). However, as mentioned in Section 5.1.2.1, insurance type may dictate whether an individual visits the doctor or a hospital, making it difficult to readily compare results between studies focusing on physician visits versus hospital admissions and ED visits.

Across $PM_{10-2.5}$ studies, a remaining uncertainty is the varying methods employed to measure ambient $PM_{10-2.5}$ concentrations (Section 2.5.1.2.3) and the subsequent impact on exposure measurement error (Section 3.3.1.1). Similar to previous hospital admission and ED visit sections, the focus of this section is on those studies that address uncertainties and limitations in the evidence as detailed in the 2009 PM ISA (U.S. EPA, 2009), such as potential copollutant confounding and model specification. For each of the studies evaluated in this section, Table 5-29 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each asthma hospital admission and ED visit study. Other recent studies of asthma hospital admissions and ED visits are not the focus of this evaluation because they did not address uncertainties and limitations in the evidence previously identified. Additionally, many of these studies were conducted in small single-cities, encompassed a short study duration, or had insufficient sample size. The full list of these studies can be found in HERO: https://hero.epa.gov/hero/particulate-matter.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 ISA. a = results for temperatures <25°C; b = results for temperatures ≥25°C. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-40 Summary of associations from studies of short-term $PM_{10-2.5}$ exposures and asthma hospital admissions and emergency department (ED) visits for a 10 μg/m^3 increase in 24-hour average $PM_{10-2.5}$ concentrations.

Table 5-29 Epidemiologic studies of $PM_{10-2.5}$ and hospital admissions, emergency department (ED) visits and physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	Mean (SD) Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
Hospital admissions				
Sheppard (2003) Seattle, WA 1987–1994 <65 yr	Average of two monitors $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	16.2	90th: 29.0	Correlation (*r*): 0.43 $PM_{2.5}$, 0.73 PM_{10}, 0.19 O_3, 0.34 SO_2, 0.56 CO Copollutant models with: NR
†Zhao et al. (2016) Dongguan, China 2013–2015 All ages	Average of five monitors $PM_{10-2.5}$ estimated by calculating the difference between PM_{10} and $PM_{2.5}$ averaged across all monitors.	18.6	75th: 22.6 Max: 96.4	Correlation (*r*): 0.42 O_3, 0.58 SO_2, 0.60 NO_2 Copollutant models with: O_3, SO_2, NO_2
†Cheng et al. (2015) Kaohsiung, Taiwan 2006–2010 All ages	Average of six monitors $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	31.7	75th: 42.1 Max: 490	Correlation (*r*): 0.64 $PM_{2.5}$, 0.89 PM_{10}, 0.24 O_3, 0.53 NO_2, 0.47 CO, 0.19 SO_2 Copollutant models with: O_3, NO_2, CO, SO_2
ED visits				
ATSDR (2006) Manhattan and Bronx, NY 1999–2000 5–18 yr; all ages	One monitor per borough $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	Manhattan: 7.1 Bronx: 7.7	NR	Correlation (*r*): NR Copollutant models with: NR
Peel et al. (2005) Atlanta, GA 1998–2000 All ages	One monitor $PM_{10-2.5}$ directly measured by a dichotomous monitor (Van Loy et al., 2000).	9.7	90th: 16.2	Correlation (*r*): NR Copollutant models with: NR

Table 5-29 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and hospital admissions, emergency department (ED) visits and physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	Mean (SD) Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
Slaughter et al. (2005) Spokane, WA 1995–1999 All ages	One monitoring site $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors.	ED visits	NR	Correlation (*r*): 0.31 $PM_{2.5}$, 0.94 PM_{10}, 0.32 CO Copollutant models with: NR
†Malig et al. (2013) 35 California counties 2005–2008 All ages	Difference of collocated PM_{10} and $PM_{2.5}$ concentration, assigned from the nearest monitoring station within 20 km of population-weighted zip code centroid.	5.6–34.4	NR	Correlation (*r*): 0.31 $PM_{2.5}$, 0.38 O_3, 0.14 CO Copollutant models with: $PM_{2.5}$, O_3, NO_2, CO, SO_2
†Strickland et al. (2010) Atlanta, GA 1993–2004 5–17 yr	Population-weighted average across monitoring site $PM_{10-2.5}$ directly measured by a dichotomous monitor (Van Loy et al., 2000).	9.0	NR	Correlation (*r*): Cold season = 0.29, 0.51, −0.05 O_3, 0.25 NO_2, 0.22 CO, 0.08 SO_2; warm season = 0.26, 0.49, 0.15 O_3, 0.36 NO_2, 0.32 CO, 0.13 SO_2 Copollutant models with: NR
Physician visits				
†Sinclair et al. (2010) Atlanta, GA 1998–2002 Children and adults	One monitor $PM_{10-2.5}$ directly measured by a dichotomous monitor (Van Loy et al., 2000).	Overall: 9.6 8/1998–8/2000: 9.7 9/2000–12/2002: 9.5	NR	Correlation (*r*): 0.43 CO warm season, 0.50 NO_2 cold season Copollutant models with: NR

CO = carbon monoxide, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤10 µm and >2.5 µm, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, PM_{10} = particulate matter with a nominal mean aerodynamic diameter ≤10 µm, *r* = correlation coefficient, SD = standard deviation, SO_2 = sulfur dioxide.

[a]All data are for 24-h average unless otherwise specified.

†Studies published since the 2009 PM ISA.

Recent studies that examine the association between short-term $PM_{10-2.5}$ exposure and asthma hospital admissions were conducted in Taiwan (Cheng et al., 2015) and China (Zhao et al., 2016). Cheng et al. (2015), in a study conducted in Kaohsiung, Taiwan, focused on whether the association between short-term $PM_{10-2.5}$ exposure and asthma hospital admissions varied if the mean temperature of each day was above or below 25°C. The authors reported positive associations similar in magnitude for both temperature ranges (≥25°C: RR = 1.02 [95% CI: 1.00, 1.05]; <25°C: RR = 1.04 [95% CI: 1.01, 1.07]). Zhao et al. (2016), in a study conducted in Dongguan, China, also reported evidence of a positive association with $PM_{10-2.5}$ that was similar in magnitude (5.5% [95% CI: 1.0, 10.2]; lag 0–3). Both Cheng et al. (2015) and Zhao et al. (2016) examined potential copollutant confounding with gaseous pollutants (i.e., NO_2, SO_2, O_3, and CO). In both studies, moderate (r, >0.4 and <0.8) to low correlations ($r < 0.4$) were reported between $PM_{10-2.5}$ and all pollutants (Table 5-29). In Cheng et al. (2015), the results from copollutant analysis were similar to those reported in the single-pollutant analyses (≥25°C: Single-pollutant, RR = 1.02, copollutant, RR = 1.01 to 1.02; <25°C: Single-pollutant, RR = 1.04, copollutant RR = 1.02 to 1.04). Zhao et al. (2016) also reported that results remained relatively unchanged in copollutant models with SO_2 and O_3, but the association with NO_2 was attenuated and uncertain (1.8% [95% CI: −2.9, 6.8]).

A limited number of epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined asthma ED visits and short-term exposure to $PM_{10-2.5}$, and were limited to single-city studies. Recent studies of ED visits consist of studies conducted in the U.S. that collectively provide evidence of a positive association between asthma ED visits and $PM_{10-2.5}$. Malig et al. (2013), in a study of 35 California counties, observed positive associations across single-day lags ranging from 0 to 2 days, with the strongest association in terms of magnitude and precision at lag 2 (3.3% [95% CI: 2.0, 4.6]) in an analysis of people of all ages. This result was found to persist when excluding extreme (i.e., highest 5%) $PM_{10-2.5}$ concentrations. Additionally, Malig et al. (2013) provided some evidence that the association between asthma ED visits and $PM_{10-2.5}$ is larger in magnitude in the warm months (quantitative results not presented). The all-year results of Malig et al. (2013) are supported by Strickland et al. (2010) in a study conducted in Atlanta, GA that focused on pediatric asthma ED visits where the authors reported a RR = 1.06 (95% CI: 1.02, 1.1) for a 0–2-day lag. However, when examining seasonal associations, the authors reported evidence that contradicts Malig et al. (2013), with associations being larger in magnitude in the cold months (RR = 1.07 [95% CI: 1.02, 1.13]) compared to the warm months (RR = 1.04 [95% CI: 0.99, 1.10]). Of the ED visit studies only, Malig et al. (2013) examined potential copollutant confounding with $PM_{2.5}$ and reported that results were robust to the inclusion of $PM_{2.5}$ in the model (3.0% [95% CI: 1.8, 4.2], lag 2).

Across both asthma hospital admissions and ED visits studies there was a rather limited assessment of the influence of model specification on the relationship with $PM_{10-2.5}$, as well as the lag structure of associations. Zhao et al. (2016) examined whether varying the degrees of freedom (df) per year to account for temporal trends and increasing the df for the temperature covariate impacted the

association between $PM_{10-2.5}$ and asthma hospital admission. In both cases, the authors reported results consistent with those observed in the main model (quantitative results not presented). Strickland et al. (2010) took a different approach to examining model misspecification by examining associations with asthma ED visits 1 day after the visit (lag −1 day), which can provide evidence of residual confounding. In an analysis limited to the warm season, the authors did not observe any evidence of potential residual confounding (RR = 1.01 [95% CI: 0.97, 1.04]). Overall, the limited association of model specification provides initial evidence indicating that models adequately account for temporal trends and the confounding effects of weather.

5.3.2.1.1 Concentration-Response Relationship

To date, very few studies have conducted analyses to examine the C-R relationship between short-term $PM_{10-2.5}$ exposure and respiratory-related hospital admissions and ED visits, including asthma. Recent studies provide a limited analysis of the C-R relationship and are limited to examining linearity without conducting a systematic evaluation of potential alternatives to linearity (Zhao et al., 2016; Malig et al., 2013), along with quintile analyses used to examine whether there is evidence that the risk of asthma ED visits changes at different $PM_{10-2.5}$ concentrations (Strickland et al., 2010).

Malig et al. (2013) examined the C-R relationship between short-term $PM_{10-2.5}$ and asthma ED visits in 35 California counties by focusing on model fit and whether replacing a linear term in the model with a squared term for $PM_{10-2.5}$ improved model fit. The authors reported no evidence of an improvement in model fit when allowing for the potential of nonlinearity in the $PM_{10-2.5}$-asthma ED visits relationship. The results of Malig et al. (2013) are consistent with Zhao et al. (2016) in a study conducted in Dongguan, China where there was evidence of a linear relationship when including a natural spline along the range of $PM_{10-2.5}$ concentrations where the data density is the highest (Figure 5-41).

Instead of examining the shape of the C-R curve, Strickland et al. (2010) conducted a quintile analysis to examine whether the association between $PM_{10-2.5}$ and asthma ED visits changed at different concentrations. For the warm season, the authors did not observe any evidence of an association when comparing each quintile to the referent (i.e., quintile 1). However, when examining the cold season, Strickland et al. (2010) reported evidence that the risk of an asthma ED visit increased as $PM_{10-2.5}$ concentrations increased, with the strongest associations observed for the 4th (RR = 1.05 [95% CI: 0.99, 1.10]) and 5th (RR = 1.08 [95% CI: 1.02, 1.14]) quintiles.